Supplementary Material

Disrupted structural connectivity of fronto-deep gray matter pathways in progressive supranuclear palsy

Alexandra Abos[1], Barbara Segura[1,2], Hugo C Baggio[1], Anna Campabadal[1], Carme Uribe[1], Alicia Garrido[3], Ana Camara[3], Esteban Muñoz[2,3,4], Francesc Valldeoriola[2,3,4], Maria Jose Marti[2,3,4], Carme Junque[1,2,4], Yaroslau Compta[2,3,4]

[1]Medical Psychology Unit, Department of Medicine. Institute of Neuroscience, University of Barcelona.Barcelona, Catalonia, Spain.

[2]Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Hospital Clínic de Barcelona. Barcelona, Catalonia, Spain.

[3]Movement Disorders Unit, Neurology Service, Hospital Clínic de Barcelona. Institute of Neuroscience, University of Barcelona, Barcelona, Catalonia, Spain.

[4]Institute of Biomedical Research August Pi i Sunyer (IDIBAPS). Barcelona, Catalonia, Spain.

***Corresponding author:** Dr. Yaroslau Compta

Supplementary Table 1A. Cortical regions of interest derived from the Desikan-Killiany atlas.

Frontal

- Superior Frontal
- Rostral and Caudal Middle Frontal
- Pars Opercularis, Pars Triangularis, and Pars Orbitalis
- Lateral and Medial Orbitofrontal
- Precentral
- Paracentral
- Frontal Pole

Parietal

- Superior Parietal
- Inferior Parietal
- Supramarginal
- Postcentral
- Precuneus

Temporal

- Superior, Middle, and Inferior Temporal
- Banks of the Superior Temporal Sulcus
- Fusiform
- Transverse Temporal
- Entorhinal
- Temporal Pole
- Parahippocampal

Occipital

- Lateral Occipital
- Lingual
- Cuneus
- Pericalcarine

Cingulate

- Rostral Anterior
- Caudal Anterior
- Posterior
- Isthmus

Insula

Supplementary Table 1B. Deep grey matter structures derived from the automated FreeSurfer segmentation atlas.

- Nucleus accumbens
- Amygdala
- Caudate nucleus
- Hippocampus
- Pallidum
- Putamen
- Thalamus
- Ventral diencephalon, including the hypothalamus, mammillary body, subthalamic nuclei, substantia nigra, red nucleus, lateral geniculate nucleus, and medial geniculate nucleus.
- Cerebellar white matter, including the middle cerebellar peduncle.

Supplementary Table 2. Forty-one significant reduced connections in PSP patients compared with HC found by TFNBS.

Cortico-DGM connections	
Right medialorbitofrontal -Left Accumbens	Left precentral -Right Caudate
Right medialorbitofrontal -Left Caudate	Left parsopercularis -Right Hippocampus
Right parsorbitalis -Left Hippocampus	Left cuneus -Right Putamen
Right precuneus -Left Hippocampus	Left lingual -Right Putamen
Right superiortemporal -Left Hippocampus	Left superiorparietal -Right Putamen
Left parsopercularis -Left Pallidum	Right parsopercularis -Right Putamen
Left parsopercularis -Left Putamen	Right parstriangularis -Right Putamen
Left parsorbitalis -Left Putamen	Left precentral -Right Thalamus
Left parstriangularis -Left Putamen	Left superiorparietal -Right Thalamus
Left parsorbitalis -Left Thalamus	Right entorhinal -Right Thalamus
Left parstriangularis -Left Thalamus	Left postcentral -Right VentralDC
Left parsorbitalis -Left VentralDC	Left precentral -Right VentralDC
Left parstriangularis -Left VentralDC	Left superiorparietal -Right VentralDC
Left parstriangularis -Left Cerebellum	Left rostralmiddlefrontal -Right Cerebellum

Cortico cortical connections	**Deep grey matter Deep grey matter connections**
Left parahippocampal -Left parsorbitalis	Left Hippocampus -Left Thalamus
Left lingual -Right parsorbitalis	Right Hippocampus -Right Thalamus
Left superiorfrontal -Right parstriangularis	Right Hippocampus -Right Cerebellum
Left precentral -Right precentral	
Left postcentral -Right precuneus	
Left superiorfrontal -Right superiorfrontal	
Right precentral -Right superiorfrontal	
Left paracentral -Right superiorparietal	
Left postcentral -Right superiorparietal	
Right lingual -Right superiortemporal	

Supplementary Table 3. Summary of the forty-one significant reduced connections in PSP patients compared with HC found by TFNBS.

Cortico-cortical tracts					
F-F	**F-P**	**F-T**	**F-O**	**O-T**	**P-P**
4	2	1	1	1	1
Cortico-Deep grey matter tracts					
F-DGM	**P-DGM**	**T-DGM**	**O-DGM**		
20	5	1	2		
Deep grey matter-Deep grey matter					
DGM-DGM					
3					
LH-LH	**RH-RH**	**LH-RH/RH-LH**			
11	4	26			

HC: healthy controls; PSP: Progressive supranuclear palsy patient group; F: Frontal; P: Parietal; T: Temporal; O: Occipital; DGM: deep grey matter structures; LH: Left hemisphere; RH: Right hemisphere.

Supplementary Table 4 A. Global graph measures in the occipital-DGM network by group

	HC (n=20)	PSP (n=19)	Stat/ p
Modularity	0.5695 (0.015)	0.5579 (0.0334)	T=1.40561/p=.2873
Clustering coefficient	1.0049 (0.005)	1.0098 (0.0147)	T=1.43800/p=.2873
Nodal degree	24.657 (0.182)	24.5182 (0.395)	T=1.42626/p=.2873
Small Worldness	1.0046 (0.005)	1.0065 (0.0113)	T=0.6939/p=.5034
Path Length	1.0003 (0.006)	1.0033 (0.009)	T=1.190621/p=.3170

HC: healthy controls; PSP: Progressive supranuclear palsy patient group; * refers to FDR corrected results; Stats refers to T-test (T).

Supplementary Table 4 B. Global graph measures in the parietal-DGM network by group

	HC (n=20)	PSP (n=19)	Stat/ p
Modularity	0.5693 (0.022)	0.5601 (0.031)	T=1.08123/p=.3292
Clustering coefficient	1.0503 (0.021)	1.0712 (0.036)	T=2.248458/p=.143
Nodal degree	27.417 (0.509)	27.077 (0.669)	T=1.78915/p=.147
Small Worldness	0.9823 (0.014)	0.9905 (0.032)	T=1.0659/p=.3292
Path Length	1.0694 (0.020)	1.0816 (0.023)	T=1.759393/p=.147

HC: healthy controls; PSP: Progressive supranuclear palsy patient group; * refers to FDR corrected results; Stats refers to T-test (T).

Supplementary Table 4 C. Global graph measures in the temporal-DGM network by group

	HC (n=20)	PSP (n=19)	Stat/ p
Modularity	0.5726 (0.014)	0.5708 (0.018)	T=0.34151/p=.724
Clustering coefficient	1.2382 (0.070)	1.2613 (0.109)	T=0.790443/p=.724
Nodal degree	30.405 (1.007)	30.175 (1.048)	T=0.69957/p=.724
Small Worldness	1.1423 (0.060)	1.1536 (0.088)	T=0.471128/p=.8353
Path Length	1.0841 (0.027)	1.0928 (0.028)	T=0.980812/p=.724

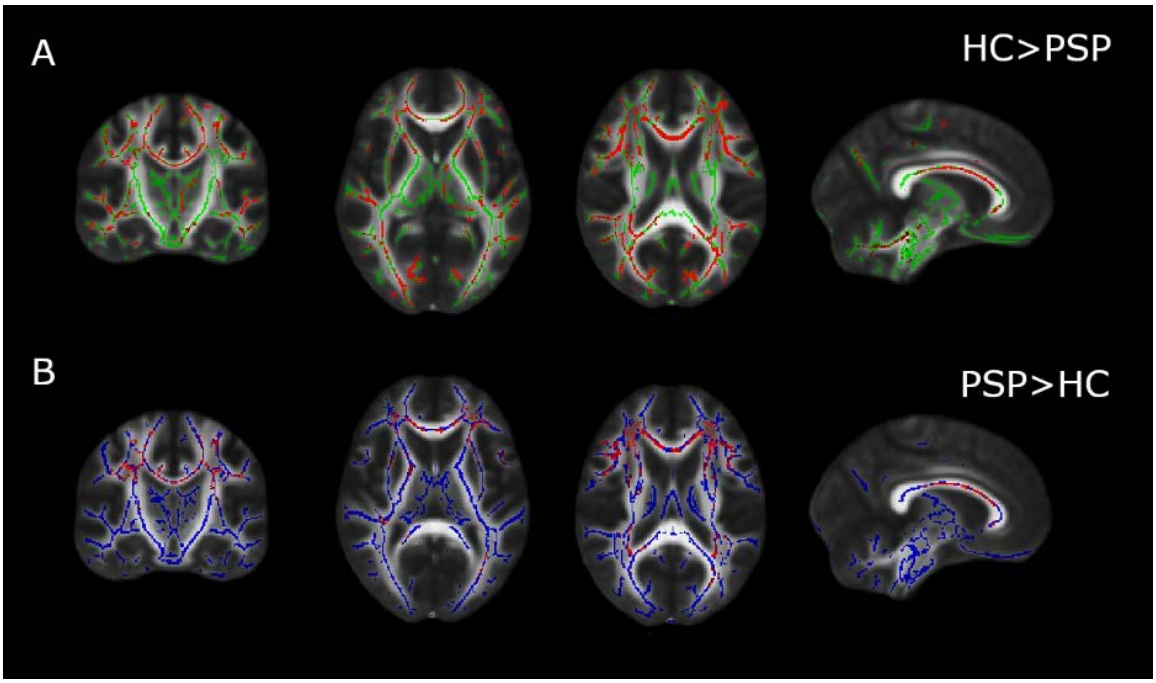
HC: healthy controls; PSP: Progressive supranuclear palsy patient group; * refers to FDR corrected results; Stats refers to T-test (T).

Supplementary Table 5. Volumetric measures (mm^3) of subcortical ROIs by group.

	HC (n=20)	PSP (n=19)	Stat/ p
Left Accumbens	469.35(101.9)	367.316(98.5)	T=3.177/p=.010*
Left Amygdala	1447.85(208.8)	1334.105(235.1)	T=1.6/p=.146
Left Caudate	3242.9(432.3)	3008.158(651.6)	T=1.332/p=.206
Left Hippocampus	3737.7(348.2)	3155.158(555.2)	T=3.95/p=.0019*
Left Pallidum	1536.75(220.1)	1245.105(238.6)	T=3.97/p=.005*
Left Putamen	4807.15(570.6)	4249.737(642)	T=2.869/p=.01*
Left Thalamus	6085.45(601.2)	5603.684(967.5)	T=2.51/p=.083*
Left Ventral DC	3782.35(434.7)	3107.474(390.8)	T=5.09/p=.0019*
Left Cerebellum	15551.7(4981.8)	12274.053(2816.9)	T=2.51 /p=.01*
Right Accumbens	539.45(97.2)	444.474(82.1)	T=3.287/p=.0063*
Right Amygdala	1498.55(183.3)	1390.789(254.3)	T=1.524/p=.152
Right Caudate	3302.2(505.5)	3038.684(786.9)	T=1.251/p=.226
Right Hippocampus	3767.25(431.2)	3238.842(522.1)	T=3.454/p=.005*
Right Pallidum	1384.7(197.5)	1189.737(239.9)	T=2.777/p=.0114*
Right Putamen	4517.9(574.9)	3973.053(669.2)	T=2.732/p=.0162*
Right Thalamus	6155.75(653.6)	5615.263(871.5)	T=2.198/p=0.0418*
Right Ventral DC	3581.05(399.1)	3127.105(357.8)	T=3.733/p=.0038*
Right Cerebellum	14149(2199.4)	12176.789(2990.5)	T=2.354/p=.0357*

HC: healthy controls; PSP: Progressive supranuclear palsy patient group; * refers to FDR corrected results; Stats refers to T-test (T).

Supplementary Figure 1. Diffusion measures maps in PSP patients compared with HC.



A. White matter maps showing regions of significant decreased fractional anisotropy (FA) in PSP patients compared with HC. B. White matter maps showing regions of significant increased mean diffusivity (MD) in PSP patients compared with HC. Background image corresponds to the mean fractional anisotropy image of all subjects in standard MNI152 space. Fractional anisotropy white matter skeleton is represented by green voxels. Mean diffusivity white matter skeleton is represented by blue voxels. Significant tracts are shown in red ($p<0.025$, bonferroni corrected). HC: healthy controls; PSP: progressive supranuclear palsy patient group.

PSP-RS subtype analyses

Of the 19 PSP patients in our samples, 15 were classified as having PSP with Richardson's syndrome (PSP-RS). No significant intergroup differences were observed between HC and PSP-RS patients for age, gender and years of education (p=0.780, p=0.148 and p=0.080, respectively).

Significant intergroup structural connectivity effects

Supplementary Figure 2 and Supplementary Table 6 show the 56 connections with significantly different NOS between groups (all $p < 0.05$, FDR corrected). Many connectivity reductions observed in PSP-RS compared with HC were also found when considering all PSP patients as a single group.

From the 56 connections, 17 (30.4%) were found to be cortico-cortical tracts, 33 (58.9%) were cortico-DGM tracts and 6 (10.7%) DGM-DGM tracts (Supplementary Table 7 and Supplementary figure 3). Concretely, fronto-DGM connections were predominantly reduced in PSP-RS compared with healthy controls. No connections showed significantly higher NOS in PSP-RS patients compared with HC.

Cortico-DGM NOS significantly correlated with PSPRS score (r=-0.509, p=0.026; see Supplementary figure 4).

Classification procedure

The LR classification algorithm correctly predicted overall group membership with an accuracy of 85%, with 100% sensitivity and 75% specificity. The 56 structural connections that showed

significant group effects when using the whole sample were obtained in more than 85% of the iterations.

Graph-metrics analyses

As shown in the main results, no group effect was found between PSP-RS and HC in global graph parameters when considering the whole-brain network (Supplementary table 8A). In the fronto-DGM subnetwork, PSP patients showed a reduced global degree (GD) (Supplementary table 8B).

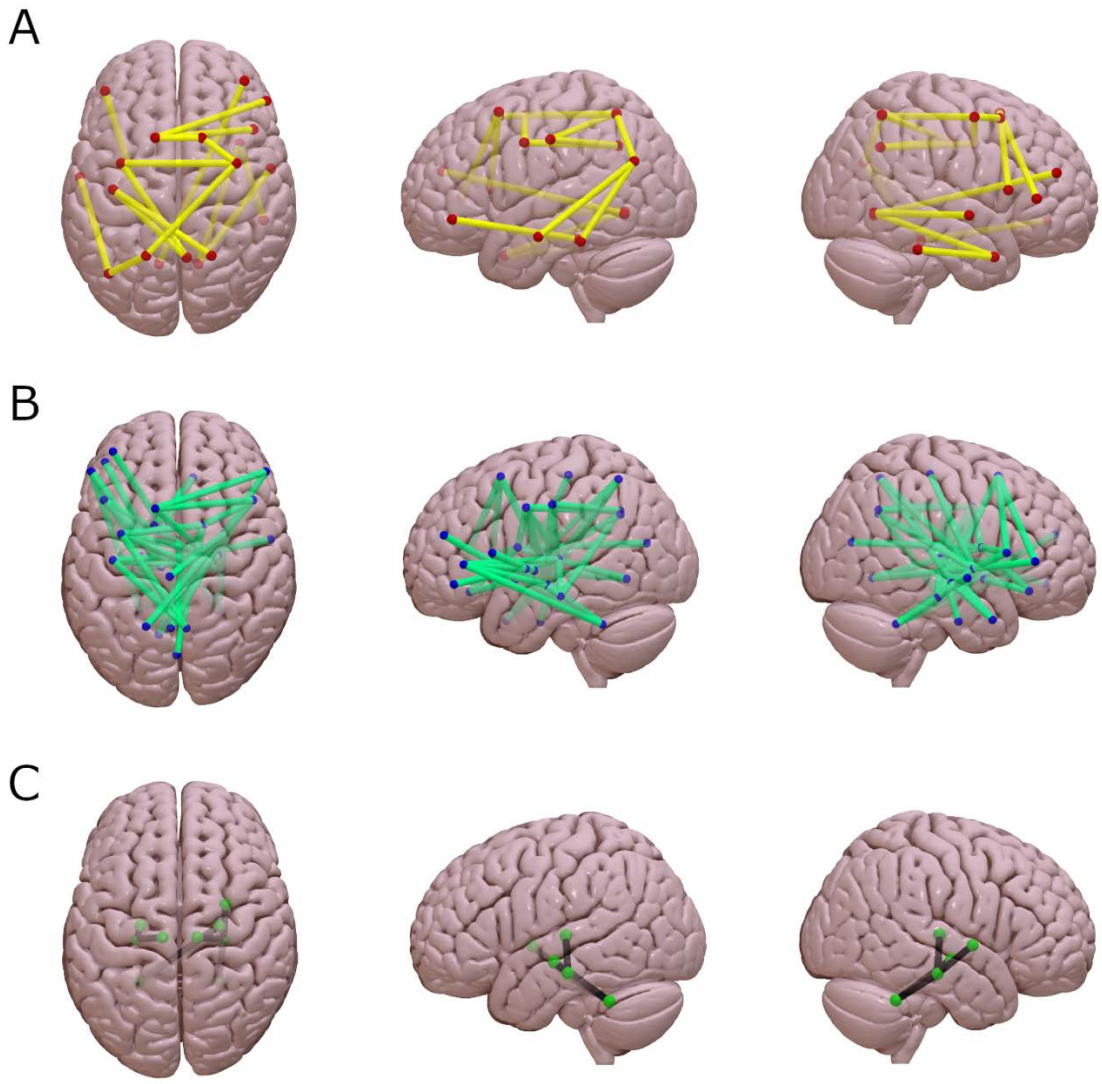
Supplementary Table 6. Fifty-six significant reduced connections in PSP-RS patients compared with HC found by TFNBS.

Cortico-cortical connections	
Left inferiorparietal-Left inferiortemporal	Left precentral-Right precuneus
Left inferiorparietal-Left middletemporal	Left lingual-Right rostralmiddlefrontal
Left parahippocampal-Left parsorbitalis	Left superiorfrontal-Right superiorfrontal
Left inferiorparietal-Left superiorparietal	Right precentral-Right superiorfrontal
Left superiorfrontal-Right parsopercularis	Left postcentral-Right superiorparietal
Left superiorfrontal-Right parstriangularis	Right lingual-Right superiortemporal
Left precentral-Right precentral	Right inferiortemporal-Right temporalpole
Left superiorparietal-Right precentral	Right lingual-Right temporalpole
Left postcentral-Right precuneus	
Cortico-DGM connections	
Right medialorbitofrontal-Left Accumbens	Left superiorfrontal-Right Hippocampus
Right medialorbitofrontal-Left Caudate	Left lingual-Right Putamen
Right precuneus-Left Hippocampus	Left paracentral-Right Putamen
Right superiortemporal-Left Hippocampus	Left precuneus-Right Putamen
Left parsopercularis-Left Pallidum	Left superiorparietal-Right Putamen
Left parsopercularis-Left Putamen	Right parsopercularis-Right Putamen
Left parstriangularis-Left Putamen	Right parstriangularis-Right Putamen
Left parsorbitalis-Left Thalamus	Left precentral-Right Thalamus
Left parstriangularis-Left Thalamus	Left superiorparietal-Right Thalamus
Left parstriangularis-Left VentralDC	Right entorhinal-Right Thalamus
Left parstriangularis-Left Cerebellum	Right temporalpole-Right Thalamus
Left cuneus-Right Caudate	Left postcentral-Right VentralDC
Left lingual-Right Caudate	Left precentral-Right VentralDC
Left precentral-Right Caudate	Left superiorparietal-Right VentralDC
Right parsopercularis-Right Caudate	Right temporalpole-Right VentralDC
Left parsopercularis-Right Hippocampus	Left rostralmiddlefrontal-Right Cerebellum
Left postcentral-Right Hippocampus	
Deep grey matter-Deep grey matter connections	
Left Hippocampus-Left-Thalamus	Right Hippocampus-Right Thalamus
Left Hippocampus-Left VentralDC	Left Cerebellum-Right VentralDC
Right Hippocampus-Right Putamen	Right Hippocampus-Right Cerebellum

Supplementary Table 7. Summary of the fifty-six significant reduced connections in PSP-RS patients compared with HC found by TFNBS.

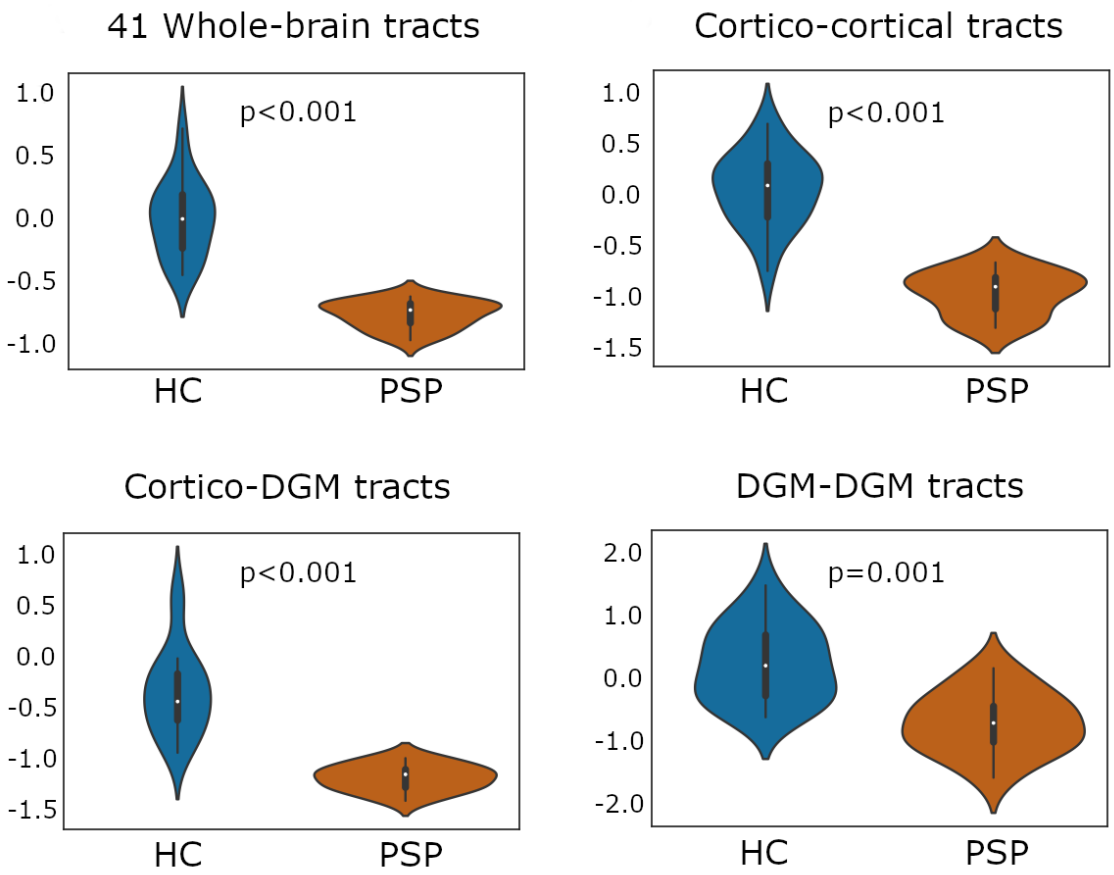
Cortico-cortical tracts							
F-F	**F-P**	**F-T**	**F-O**	**O-T**	**P-P**	**P-T**	**T-T**
5	3	1	1	2	2	2	1
Cortico-Deep grey matter tracts							
F-DGM	**P-DGM**	**T-DGM**	**O-DGM**				
19	7	4	3				
Deep grey matter-Deep grey matter							
DGM-DGM							
6							
LH-LH	**RH-RH**	**LH-RH/RH-LH**					
13	14	29					

HC: healthy controls; PSP-RS: Richardsonian progressive supranuclear palsy patient group; F: Frontal; P: Parietal; T: Temporal; O: Occipital; DGM: deep grey matter structures; LH: Left hemisphere; RH: Right hemisphere.



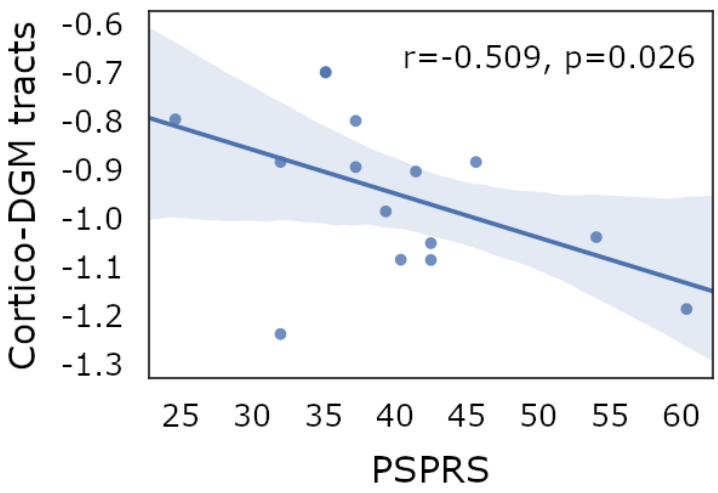
Supplementary Figure 2. *Schematic representation of the 56 structural connections with reduced structural connectivity strength in progressive supranuclear palsy patients with Richardson's syndrome (PSP-RS) compared with healthy controls using threshold-free network based statistics.*

A. Connectivity differences between groups in cortico-cortical tracts ($p < 0.05$, FDR corrected). B. Connectivity differences between groups in cortico-deep gray matter tracts ($p < 0.05$, FDR corrected). C. Connectivity differences between groups in deep gray matter-deep gray matter tracts ($p < 0.05$, FDR corrected). Connectivity figures were drawn using Surf Ice (www.nitrc.org).



Supplementary Figure 3. *Comparison of global graph metrics between progressive supranuclear palsy patients with Richardson's syndrome and healthy controls in the fronto-deep gray matter subnetwork.*

Plots illustrate the distribution of the nodal degree, clustering coefficient, path length, small worldness and modularity in the fronto-deep gray matter subnetwork between groups. Significance of intergroup analyses ($p < 0.05$, FDR corrected) are shown. HC: healthy controls; PSP-RS: progressive supranuclear palsy with Richardson's syndrome group.



Supplementary Figure 4. *Relationship between structural connectivity and PSPRS in progressive supranuclear palsy patients with richardsonian subtype.*

Significant correlation between the mean NOS Z-score from the cortico-DGM reduced connections in PSP-RS patients and the PSPRS scale.

Supplementary Table 8A. Whole-brain global graph measures by group

	HC (n=20)	PSP (n=15)	Stat/ p
Modularity	0.5197 (0.013)	0.5198 (0.165)	T=0.0295/p=.8412
Clustering coefficient	1.4638 (0.103)	1.5190 (0.127)	T=1.4190/p=.2636
Nodal degree	68.295 (2.367)	66.612 (2.982)	T=1.8662/p=.2620
Small Worldness	1.301 (0.083)	1.3414 (0.103)	T=1.2804/p=.2630
Path Length	1.1247 (0.016)	1.1319 (0.017)	T=1.2676/p=.2630

HC: healthy controls; PSP: Progressive supranuclear palsy patient group; Stats refers to Student's t-test (T).

Supplementary Table 8B. Global graph measures in the fronto-DGM network by group

	HC (n=20)	PSP (n=15)	Stat/ p
Modularity	0.4826 (0.021)	0.4780 (0.026)	T=0.5832/p=.6154
Clustering coefficient	1.608 (0.045)	1.206 (0.075)	T=2.1885/p=.0610
Nodal degree	33.862 (0.793)	32.703 (1.230)	T=3.3877/p=.0190*
Small Worldness	1.087 (0.037)	1.1246 (0.057)	T=2.3636/p=.0590
Path Length	1.068 (0.017)	1.0717 (0.026)	T=0.5134/p=.6154

HC: healthy controls; PSP: Progressive supranuclear palsy patient group; DGM: Deep gray matter structures; * refers to FDR corrected results; Stats refers to Student's t-test (T).