PN 239

WHITE MATTER CONNECTOME IN PATIENTS WITH GENETIC DYSTONIA

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INTRODUCTION AND OBJECTIVE

✓Primary dystonia (DYT) has tradionally been attributed to basal ganglia dysfunction. Recent studies expanded this picture suggesting primary DYT as a circuit disorder. Aim of this study is to investigate structural neural pathways in clinically manifesting and non-manifesting individuals with several DYT genotypes using a network approach.

METHODS

✓This study included a large series of clinically manifesting and non-manifesting DYT mutation carriers. Specifically, we enrolled 9 asymptomatic mutation carriers (4 DYT1, 4 DYT6, 1 DYT10) and 26 symptomatic mutation carriers (7 DYT1, 7 DYT6, 9 DYT5 or dopa-responsive dystonia, 1 DYT18, 1 DYT10, and 1 DYT25). 37 age- and sex-matched healthy controls (HC) were also studied.

Table 1. Demographic and clinical findings in healthy controls and in patients with symptomatic and asymptomatic genetic DYT.

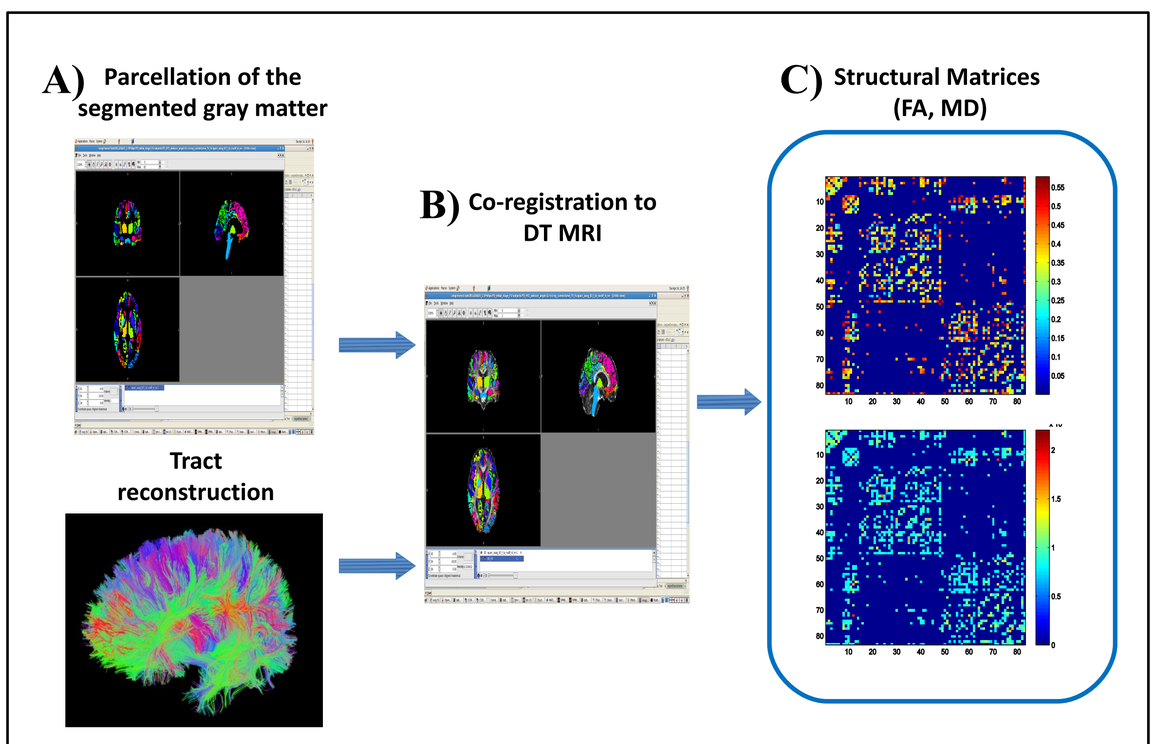
	HC	DYT-S	DYT-A	p*	p#	p§
Number	37	26	9			
Age [years]	41.40 ± 12.24	39.65 ± 13.52	45.08 ± 15.17	1.00	1.00	0.87
Gender [F/M]	24/13	15/11	7/2	0.70	0.46	0.34
Education [years]	14.49 ± 2.54	12.12 ± 2.32	11.00 ± 5.13	0.007	0.008	1.00
FMS [0-120]	-	8.80 ± 8.70	-	-	-	-
UDRS [0-112]	-	14.80 ± 11.92	-	-	-	-

Abbreviations: HC= healthy controls; DYT-S= symptomatic dystonic patients; DYT-A= asymptomatic dystonic patients; F= females; M= males; FMS= Fahn-Marsden Scale; UDRS= Unified Dystonia Rating Scale.
P values refer to ANOVA models, followed by post-hoc pairwise comparisons. p*: DYT-S *vs* healthy controls; p#: DYT-A *vs* healthy controls; p§: DYT-S *vs* DYT-A.
DYT5 patients were not included in FMS and UDRS statistics.

MRI acquisition and preprocessing.

✓Subjects underwent 3D T1 weighted and diffusion tensor (DT) MRI. The human macroscale connectome – a comprehensive map describing all neural connections between large-scale brain regions – was constructed from DT MRI.

✓Tissue segmentation was performed on T1 images using Freesurfer (v. 5.3).



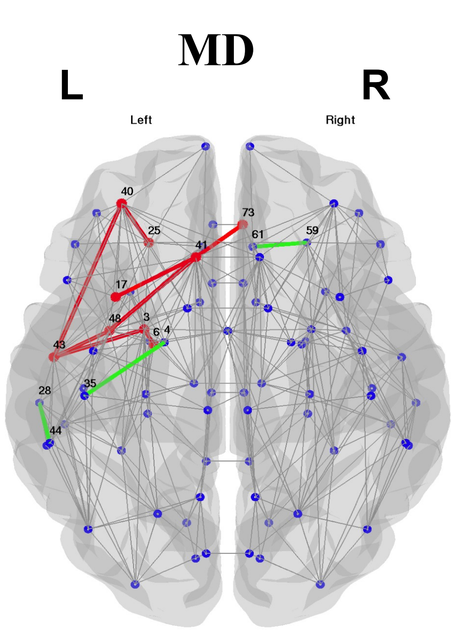
A) Parcellation of the segmented gray matter mask into 83 distinct brain regions based on Desikan atlas including basal ganglia. DT MRI tractography was performed to reconstruct the white matter tracts forming the structural network.
B) Parcellated gray matter was co-registred to subject DT MRI.
C) From the total collection of reconstructed streamlines those that touched both region *i* and *j* were selected. Then, from the selected fiber streamlines, the average fractional anisotropy (FA) and mean diffusivity (MD) values were computed as the average over all points. This value was incorporated into cell c(*i*,*j*) in the matrix.

✓The affected structural connections in subjects with manifesting and non-manifesting DYT relative to healthy controls and each other were investigated using Network-Based Statistic ($p<0.01$, 10.000 permutations).

RESULTS

✓Clinically manifesting DYT mutation carriers relative to healthy subjects showed an altered subnetwork characterized by increased mean diffusivity (MD) connecting left putamen, middle and superior frontal gyri, orbitofrontal cortex, middle temporal gyrus, insula and right anterior cingulate cortex.

DYT-S *vs* HC



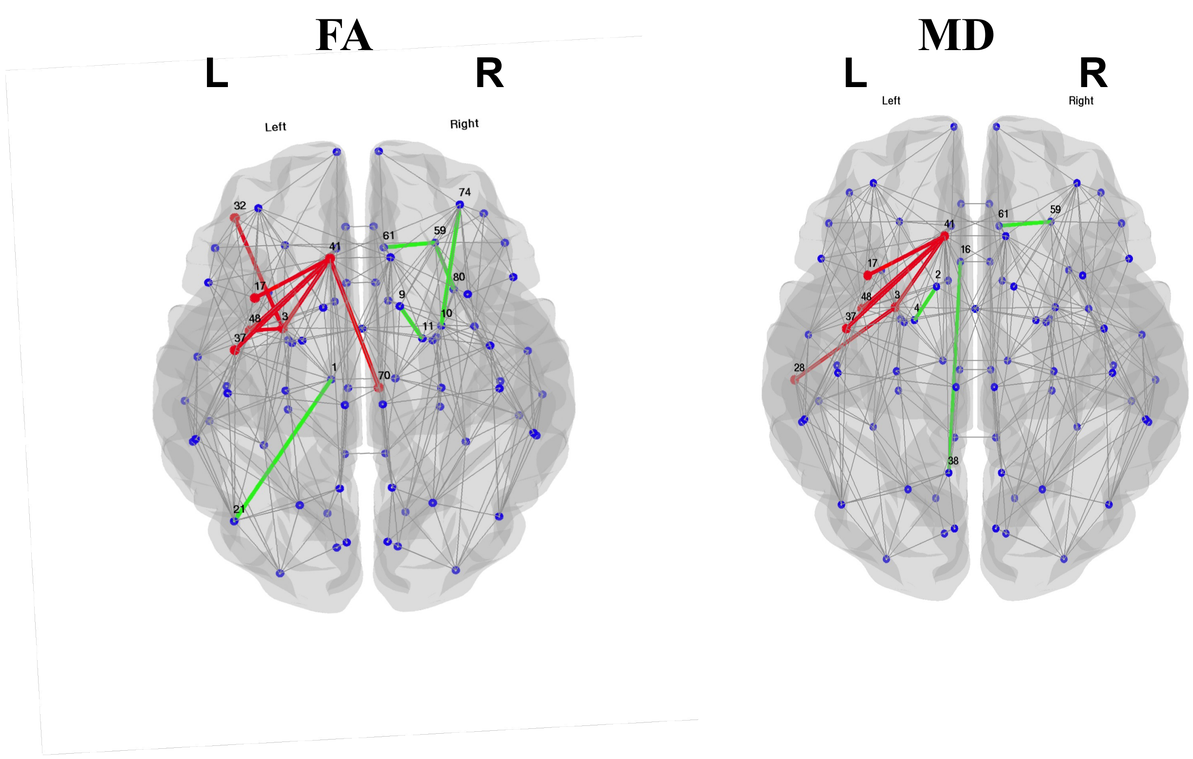
Nodes

1	L-Thalamus
2	L-Caudate
3	L-Putamen
4	L-Pallidum
6	L-Amygdala
9	R-Caudate
10	R-Putamen
11	R-Pallidum
16	L-caudal anterior cingulate
17	L-caudal middle frontal
21	L-inferior parietal
25	L-lateral orbitofrontal
28	L-middle temporal
32	L-pars orbitalis
37	L-precentral
40	L-rostral middle frontal
41	L-superior frontal
43	L-superior temporal
44	L-supramarginal
48	L-insula
59	R-lateral orbitofrontal
61	R-medial orbitofrontal
69	R-postcentral
70	R-posterior cingulate
73	R-rostral anterior cingulate
80	R-temporal pole

Principal connected component
Other affected components

✓When compared to controls, asymptomatic mutation carriers showed a basal ganglia/frontal subnetwork with decreased fractional anisotropy (FA) and increased MD including the left putamen, precentral gyrus, middle and superior frontal gyri, middle temporal gyrus, and insula.

DYT-A *vs* HC



✓No differences were found between symptomatic and asymptomatic DYT subjects.

DISCUSSION AND CONCLUSIONS

✓Our findings suggest that structural brain abnormalities in both clinically manifesting and non-manifesting DYT mutation carriers are distributed at a network level, beyond the basal ganglia/sensorimotor cortex regions.

✓The identified subnetworks include dorsal frontal, insular and temporal cortices along with the basal ganglia and primary motor cortex.

✓Studying of non-manifesting gene-positive individuals (past the age of clinical onset) offered us the possibility of identifying genotype-related trait characteristics without the confound of clinical symptoms.

✓We conclude that analyzing the affected structural subnetworks may provide new insights into understanding dystonia generation.