Aberrant brain network connectivity assessed using graph theory in paroxysmal kinesigenic dyskinesia

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Purpose: Paroxysmal kinesigenic dyskinesia (PKD) is a rare movement disorder that is characterized by sudden, brief attacks of involuntary movements that are precipitated by sudden voluntary movement. Though there are no apparent morphological changes in patients with idiopathic PKD, the dysfunction of the basal ganglia and thalamus together with impaired somatosensory intracortical inhibition are proposed as the pathophysiological basis of the disease [1]. The purpose of this study is to detect the topological organization of whole-brain connectivity and the information integration capacity between basal ganglia and cortical regions in PKD using graph theoretical approaches.

Materials and Methods: We recruited 36 patients with idiopathic PKD, mean age at initial onset was 11.4 ± 3.2 (range 3–19) years, and the mean disease duration was 13.0 ± 7.0 (range 3–29) years. Fifty-one age- and sex-matched controls were also recruited. The whole-brain functional networks were constructed by thresholding partial correlation matrices of 90 brain regions, and graph theory-based approaches were then performed to investigate their aberrant topological properties (e.g., small-world, efficiency, and nodal centrality). Nonparametric permutation tests were further used for group comparisons of topological metrics using the false discovery rate (FDR) correction.

Results: Both the patients and controls showed small-world topology in brain functional networks. However, the patients showed significantly increased clustering coefficient Cp, local efficiency E_{loc}, global efficiency E_{glob}, and normalized characteristic path length λ; while significantly decreased characteristic path length L_p (Fig. 1). Furthermore, the patients exhibited enhanced nodal centralities in the bilateral insula, putamen, and pallidum (Fig. 2). The altered nodal centrality in right insula was positively correlated with age (R=0.35, P=0.03), while no significant correlation was found between age of onset, gender, frequency of attack and duration of the disease with any of regions with altered nodal centralities.

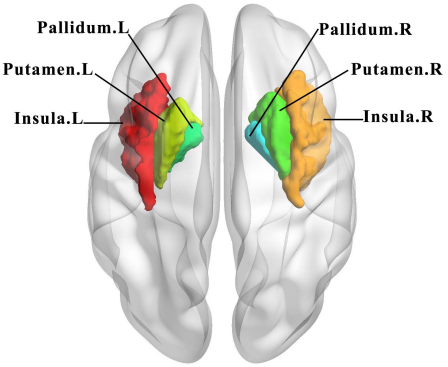

Fig. 2: Brain regions showing abnormal nodal centralities in brain functional networks: bilateral insula, putamen, and pallidum (P<0.05, FDR corrected).

Discussion: The PKD patients exhibited a much more active organization pattern functionally organized in a small-world fashion characterized by higher local specialization and global integration than controls. This finding may contribute to the pathophysiology of PKD; the transient attacks of choreoathetosis or dystonia may be related to the enhanced local and global connectivity. Moreover, the patients exhibited enhanced nodal centralities in the basal ganglia including bilateral putamen and pallidum, which is consistent with findings of abnormalities in the basal ganglia-thalamo-cortical motor circuits in PKD patients in previous studies [2].

Conclusion: Global and local functional networks are altered in PKD with altered brain regions are located in basal ganglia. As dystonia is commonly viewed as a sequence of basal ganglia dysfunction, our results support the basal ganglia theory for pathophysiological mechanisms of PKD, accounting for the hyperexcitable phenomenon in patients. Overall, our results demonstrated for the first time that PKD is reflected in an aberrant topological organization in basal ganglia-cortical functional brain network thus providing valuable information for better understanding the pathogenesis of this disorder.

References:

[1] Kailash P. Bhatia., Mov Disord, 2011, Vol. 26. No.6. [2] Nambu A. et al., Front Syst Neurosci, 2011, Nov; 5:89.

Table 1. Clinical characteristics of patients with paroxysmal kinesigenic dyskinesia (data were shown with 16 patients)

No.	Sex	Age	Age at onset	Duration of disease	Family history	Attack frequency	Affected side	Type of dyskinesia
1	M	22y	10y	11y	+	7-10/day	Bilateral	Dystonia
2	M	25y	19y	7y	_	0-5/day	Right	Dystonia
3	M	22y	11y	11y	_	0-1/day	Left	Dystonia
4	F	19y	12y	7y	_	10-20/day	Left	Dystonia
5	M	19y	14y	5y	_	10-20/day	Bilateral	Dystonia
6	M	36y	9y	28y	+	3-10/day	Bilateral	Choreoathetosis
7	M	37y	11y	25y	+	3-5/day	Bilateral	Choreoathetosis
8	M	24y	8y	16y	+	10-20/day	Bilateral	Choreoathetosis
9	M	33y	12y	21y	_	3-4/day	Left	Dystonia
10	M	26y	7y	19y	_	10-20/day	Bilateral	Choreoathetosis
11	F	20y	17y	3y	_	2-3/day	Bilateral	Dystonia
12	M	19y	13y	6y	+	1-2/day	Left	Dystonia
13	F	21y	13y	8y	+	3-5/day	Bilateral	Dystonia
14	M	26y	3y	23y	+	2-3/day	Bilateral	Dystonia
15	M	21y	9y	12y	_	5-8/day	Right	Dystonia
16	M	30y	10y	20y	_	15/day	Left	Choreoathetosis

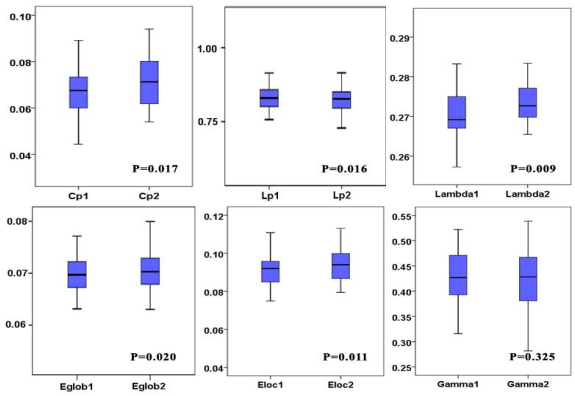

Fig. 1: Differences in topological properties of functional brain networks between PKD patients and controls.