Effects of PRRT2 mutation on brain gray matter networks in patients with paroxysmal kinesigenic dyskinesia

Xiuli Li[a], Du Lei[a,b], Kun Qin[a], Lei Li[a], Yingying Zhang[c], Dong Zhou[c], Graham J. Kemp[d], Qiyong Gong[a]

Author Affiliations:

[a] Huaxi MR Research Center (HMRRC), Department of Radiology, West China Hospital of Sichuan University, Chengdu, Sichuan Province, China

[b] Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati, Cincinnati, Ohio, USA

[c] Department of Neurology, West China Hospital of Sichuan University, Chengdu, Sichuan Province, China

[d] Liverpool Magnetic Resonance Imaging Centre (LiMRIC) and Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool, U K

Correspondence to:

Prof. Qiyong Gong, Huaxi MR Research Center (HMRRC), Department of Radiology, West China Hospital of Sichuan University, No. 37 Guo Xue Xiang, Chengdu, Sichuan 610041, PR China. Tel.: +86 28 81812593; Fax: +86 28 85423503.

E-mail: qiyonggong@hmrrc.org.cn

Prof. Dong Zhou, Department of Neurology, West China Hospital of Sichuan University, No. 37 Guo Xue Xiang, Chengdu, Sichuan 610041, PR China

E-mail: zhoudong66@yahoo.de

Abstract

Objective: PRRT2 has been identified as the causative gene for paroxysmal kinesigenic dyskinesia (PKD). However, the underlying neural mechanisms are unclear. The aim of this study was to explore the effects of PPRT2 on gray matter structural networks in PKD.

Methods: We recruited 51 PKD patients with PRRT2 mutation (PKD-M), 55 PKD patients without PRRT2 mutation (PKD-N), and 80 healthy controls (HC). We analyzed individual gray matter structural networks based on structural T1-weighted imaging. We compared the structural connectome characteristics across groups, and applied a support vector machine to classify PKD-M *vs* PKD-N.

Results: Relative to PKD-N and HC, PKD-M showed significant decrease in global and local efficiency and increase in characteristic path length. Relative to HC, both patient groups showed significantly decreased nodal centralities and structural connections in right postcentral gyrus, right angular, bilateral thalamus, and left median cingulate and paracingulate gyri; relative to both PKD-N and HC, PKD-M showed altered (almost all decreased) nodal centralities and structural connections in the cortico-basal ganglia-thalamo-cortical network including bilateral supplementary motor area, right caudate nucleus and bilateral pallidum. Finally, using the structural network matrices to classify individuals as PKD-M *vs* PKD-N, we achieved 74.3% accuracy.

Conclusions: PKD-M showed a global network pattern of "weaker small-worldness" and more extensive local (regional) disturbance in the cortico-basal ganglia-thalamo-cortical circuit; these PRRT2-related network traits may throw light on how PRRT2 mutations affect PKD by modulating these networks. Our findings provide insight into the neuropathophysiology of PKD.

Keywords: Paroxysmal kinesigenic dyskinesia, PRRT2, Similarity-based gray matter network, Graph theory, cortico-basal ganglia-thalamo-cortical circuit

1 INTRODUCTION

Paroxysmal kinesigenic dyskinesia (PKD) is the commonest hereditary paroxysmal movement disorder, characterized by recurrent brief involuntary hyperkinesias including dystonia, choreoathetosis, ballismus or a combination of these, with preserved consciousness (Bhatia, 2011; Bruno et al., 2004; Ebrahimi-Fakhari, Saffari, Westenberger, & Klein, 2015); these typically are triggered by sudden voluntary movements and appear more often during stress and anxiety (Ebrahimi-Fakhari, Moufawad El Achkar, & Klein, 2018; Ebrahimi-Fakhari et al., 2015). Pathophysiological understanding of PKD was advanced considerably by the discovery of its association with mutations in the proline-rich transmembrane protein 2 (PRRT2) (W. J. Chen et al., 2011). Mutations in PRRT2 are considered the leading cause of PKD (Lee et al., 2012; J. Li et al., 2012; Méneret et al., 2012) and considerable efforts have been devoted to studies of its normal function and its dysfunction in PKD.

PRRT2 encodes a neuronal protein highly expressed in the central nervous system, with an important role in synapse development and function, especially neuronal migration, spinogenesis, synapse formation and maintenance, and neurotransmitter release (Liu et al., 2016; Valente et al., 2016; Valtorta, Benfenati, Zara, & Meldolesi, 2016). Most reported mutations in PRRT2 lead to a truncated or absent protein: at the cellular level this affects synaptic neurotransmitter release and neuronal excitability in various brain regions (Ebrahimi-Fakhari et al., 2018; Ebrahimi-Fakhari et al., 2015), resulting in abnormal activity and functional connectivity (Long et al., 2017; Luo et al., 2013). However, the neural mechanisms remain under-explored.

MRI-based brain connectome analysis is a useful way to quantify altered brain networks in neuropsychiatric disorders. The main current approaches to the brain structural connectome are diffusion tensor imaging (DTI) or structural MRI for white matter networks (Iturria-Medina et al., 2007) and structural MRI regional covariance

analysis for gray matter networks (Tijms, Seriès, Willshaw, & Lawrie, 2012). The PRRT2 mutation affects the MRI-based white matter structural network (L. Li et al., 2020). The DTI-based structural connectome is affected by selection of tractography algorithms and poses technical challenges in estimating the connectivity strength of long-distance projections (Donahue et al., 2016). A different, technically robust approach to gene-related topological organization is to study gray matter structural networks: these are genetically heritable (Alexander-Bloch, Giedd, & Bullmore, 2013; Elman et al., 2017; Richmond, Johnson, Seal, Allen, & Whittle, 2016) and can identify stable phenotypes (Novellino et al., 2019; W. Zhang et al., 2020). A useful feature is that, instead of creating a single network of anatomical covariance for a group of participants, a similarity-based gray matter network can constructed for each individual, providing an opportunity to examine associations of network metrics with behavioral characteristics (Tijms et al., 2012).

In this study, we compared the topological organization of similarity-based gray matter structural networks between patients with and without a PRRT2 mutation in order to isolate its effect on these networks. We wished to test three hypotheses. (1) Given the evidence from white matter network studies of weaker 'small-world organization' in patients with PRRT2 mutations (L. Li et al., 2020), we hypothesized that similar disruptions would also characterize the similarity-based gray matter networks. (2) As alterations in the cortico-basal ganglia-thalamo-cortical network have been most consistently reported in PKD (Kim, Kim, Kim, Suh, & Koh, 2015; X. Li et al., 2021; Zhou et al., 2010), we hypothesized that these regions would show the more severe nodal abnormalities in patients with PRRT2 mutations. (3) As we found that gray matter morphological network matrices can classify PKD *vs* HC (X. Li et al., 2021), we hypothesized that gray matter structural network matrices could also discriminate patients with and without a PRRT2 mutation.

2 MATERIALS AND METHODS

2.1 Participants

106 patients with PKD were recruited from 2013-21 in the Department of Neurology, West China Hospital of Sichuan University. All were diagnosed according to the accepted criteria (Bruno et al., 2004). To exclude secondary PKD, routine MRI, electroencephalogram, and laboratory tests including plasma electrolytes, parathyroid hormone and ceruloplasmin were conducted. Also excluded were patients with any history of alcohol/drug abuse, psychiatric or neurological disorders, or brain lesions on routine MRI. After genetic testing, patients were further classified into 2 subgroups: 51 PKD patients with PRRT2 mutations (PKD-M) and 55 PKD patients with no PRRT2 mutations (PKD-N). We recruited 80 healthy controls (HCs) matched to the PKD group for age, gender and handedness from the local area by poster advertisement. Demographic and clinical data are shown in Table 1. Written informed consent was obtained from all the participants or their legal guardians. The study was approved by the local human research ethics committee.

2.2 Genetic analysis

In PKD patients, genomic DNA was extracted from the peripheral blood using a standard phenol/chloroform extraction method. Sanger sequencing was used to detect PRRT2 mutations using an ABI 3730 automated DNA sequencing system (details in Supplementary Materials). The results were used to subdivide the patients into two groups: PKD-M and PKD-N.

2.3 MRI data acquisition

MRI scans were performed on a 3.0-T MR imaging system (Siemens Trio, Erlangen, Germany). The head was stabilized with foam padding. High-resolution 3D T1-weighted images were acquired using a magnetization-prepared rapid gradient-echo sequence with the following parameters: resolution 1.0 × 1.0 × 1.0 mm; repetition time/echo time 1,900/2.26 ms; inversion time 900 ms; flip angle 9°; field of view 256

× 256 mm^2; 176 sagittal slices 1 mm thick; voxel size 1 × 1 × 1 mm^3. Total acquisition time was 420 s.

2.4 MRI data preprocessing

Structural images were preprocessed using the automated quantitative morphological analysis technique of voxel-based morphometry (VBM) (Ashburner & Friston, 2000) as implemented in Statistical Parametric Mapping version 12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). First, the MRI data for each participant were checked by two neuroradiologists to ensure that there were no scanning artifacts or structural abnormalities. Second, the individual structural data were segmented into gray matter, white matter and cerebrospinal fluid using the unified segmentation tool (Ashburner & Friston, 2005). Next, the resultant gray matter images were normalized to the Montreal Neurological Institute coordinate space using a high-dimensional "Diffeomorphic Anatomical Registration Through Exponential Lie Algebra" approach (Ashburner, 2007) and further nonlinearly modulated to compensate for spatial normalization effects. Lastly, all modulated GM images were resampled to 2 × 2 × 2 mm^3 voxels and individually smoothed with a 6 mm full-width at half-maximum (FWHM) Gaussian kernel. The smoothed and modulated GM images went on to further analysis.

2.5 Extraction of gray matter networks

For each participant similarity-based gray matter structural networks were obtained using a completely automated data-driven method (Tijms et al., 2012). The network nodes were defined as regions of interest (ROI) corresponding to 3 × 3 × 3 mm^3 cubic voxel cubes, and the network edges as the statistically similar gray matter morphology of each pair of cubes, quantified by correlation coefficients. Next, weighted networks were constructed after determining a threshold for each individual graph with a permutation-based method to ensure a significant similarity ($p < 0.05$) for all individuals (Weese, Rsch, Netsch, Blaffert, & Quist, 1999); only positive similarity values survived this threshold. As these similarity-based gray matter structural

networks can have different sizes, and size *per se* can effect network properties (van Wijk, Stam, & Daffertshofer, 2010), we normalized them using a method (Batalle et al., 2013) based on the unified Automated Anatomical Labeling (AAL) parcellation template (Tzourio-Mazoyer et al., 2002): each cube in the similarity-based network was linked to the AAL atlas region to which most of its voxels belonged, so that each subject ended up with 90 nodes, corresponding to the 90 brain regions of the AAL atlas. Each pair of nodes was considered to be connected with a weight (0-1) defined as the ratio of the sum of actual significant correlations to the total possible connections between all the other nodes belonging to the two ROIs (excluding self-connections). This yielded a 90×90 weighted normalized network of brain structures for each participant.

2.6 Graph-based Network Analysis

The topological properties of brain gray matter networks were calculated using GRETNA software as in previous studies (J. Wang et al., 2015; Zhang et al., 2011; Zhao et al., 2020). We applied a wide range of sparsity (S) thresholds to all the correlation matrices to ensure that the threshold networks were estimable for small-worldness with sparse properties and had the minimum number of spurious edges. This was determined using two criteria: (1) the average node degree (the number of all edges connected to a node) of each threshold network degree is > 2log (N) (where N is 90, the number of nodes); and (2) the small-world scalar σ of the threshold network of all subjects (as defined below) is >1.1 (Watts & Strogatz, 1998). With these criteria, the range of threshold was $0.10 < S < 0.34$ with an interval of 0.01. For each network metric the area under the curve (AUC) across the sparsity parameter S provides a summarized scalar for avoiding an arbitrary single threshold selection (He et al., 2009; Zhang et al., 2011).

Both global and nodal network properties were calculated for the brain networks at each sparsity threshold. For global properties: clustering coefficient (Cp), characteristic path length (Lp), normalized clustering coefficient (γ), normalized characteristic path length (λ), small-worldness (σ), local efficiency (Eloc) and global efficiency (Eglob). For nodal properties: nodal efficiency and nodal degree. Details of these are provided in Supplementary Materials.

2.7 Statistical analysis

2.7.1 Comparison of demographic and clinical variables

Differences in demographic data among PKD-M, PKD-N, and HC were compared by one-way analysis of variance (ANOVA) (age and education years) and chi-square test (gender). Differences in demographic data (age, education years, age of onset and illness duration) between PKD-M and PKD-N were analyzed with two-sample t test using IBM SPSS version 21.0.

2.7.2 Comparison of network metrics

Between-group differences in the AUC of network metrics were compared using nonparametric permutation tests (10,000 permutations) with a design model of one-way ANOVA using GRETNA software followed by *post hoc* tests using IBM SPSS version 21.0 (T. Chen et al., 2017; Zhang et al., 2011). To address multiple comparisons of nodal metrics, we applied false discovery rate (FDR) in ANOVA and *post hoc* tests at a significance value of 0.05 (Benjamini, Drai, Elmer, Kafkafi, & Golani, 2001).

2.7.3 Network-based statistical analysis

Any alteration in regional nodal metrics indicates an alteration in similarity with other nodes. We used a network-based statistics (NBS) approach to identify the specific altered gray matter correlations associated with nodes showing altered metrics between the PKD-M, PKD-N and HC groups (Zalesky, Fornito, & Bullmore, 2010). First, we chose nodes that exhibited significant intergroup differences in at least one of the nodal centralities (nodal degree and nodal efficiency), and for each participant created a connection matrix based on these altered nodes . An NBS approach was then applied to define a set of suprathreshold links that included any connected components ($p < 0.05$, FWE-corrected network level). The threshold t value was 3.0 and the number of permutations was 10,000.

2.7.4 Correlations with clinical variables

After significant group differences were identified in the network metrics, we assessed the relationships between altered network metrics and the age of onset and illness duration in the two patient groups by using partial correlations with age, gender, and education as covariates, using SPSS.

2.7.5 Support vector machine (SVM) analysis

To determine how well these measures can distinguish individual PKD patients with or without PRRT2 mutations, we applied an SVM analysis using gray matter structural network matrices to classify patients in one or the other group. We used the SVM implementation from the Scikit-Learn library (Pedregosa et al., 2012) based on LIBSVM (Chang & Lin, 2011). The model maps the input data from the training set to the feature space using a set of mathematical functions known as kernels (a linear kernel was preferred to minimize the risk of overfitting). In this feature space, the model then learns the optimum separation surface maximizing the margin between different classes.

We used a 10-fold stratified cross-validation scheme to assess the reliability of the model. The 106 patients were divided into 10 nonoverlapping partitions, each with the same proportion of PRRT2 positive and negative. Nine partitions (96 subjects) were used as the training set, then the trained model was used to make predictions for the remaining partition, the test set (10 subjects). We performed a nested cross-validation inside the training set (i.e. 10-fold stratified nested cross-validation) to select the optimum C value for the SVM, by performing a grid search in the range of values C = 10−3, 10−2, 10−1, 10^0, 10^1, 10^2, 10^3, 10^4. After selecting the optimum C, an SVM trained with the whole training set was used to assess performance on the test set in terms of balanced accuracy, specificity, and sensitivity (unbiased estimates, since the test set was not part of the training process). As these estimates are the mean values calculated on each partition of the cross-validation scheme, to estimate the significance for each SVM, a nonparametric permutation test (1,000 permutations) was performed to calculate a *p* value for balanced accuracy (Golland & Fischl, 2003). The code used is available at http://github.com/Warvito/integrating-multi-modal-neuroimaging.

3.RESULTS

3.1. Demographic and Clinical Characteristics

The demographic and clinical data are summarized in Table 1. There were no significant differences in age and gender between the three groups ($P > 0.05$). The PKD-M group showed earlier onset ($P = 0.013$), longer illness durations ($P = 0.002$), longer attack duration ($P < 0.001$) and more tendency for a family history ($P < 0.001$) than PKD-N.

3.2 Global brain network properties

In the defined threshold range, all patients and controls showed a higher normalized clustering coefficient ($\gamma > 1$) and similar normalized characteristic path length ($\lambda \approx 1$) compared to random reference networks, indicating small-world topology ($\gamma/\lambda > 1$) (Figure S1). The ANOVA and *post hoc* analyses revealed significant differences in PKD-M compared to HC (decreased global efficiency (Eglob), decreased local efficiency (Eloc), increased characteristic path length (Lp)) and in PKD-M compared to PK-N (decreased Eglob increased Lp). There were no significant differences in other global topological properties (Table 2 and Figure S2).

3.3 Nodal brain network properties.

The ANOVA analyses identified significant differences among the three groups in 13 regions which showed significant between-group differences in at least one nodal metric. In *post hoc* tests both patient groups, relative to HC, showed decreased nodal centralities in right postcentral gyrus, right angular, bilateral thalamus, and left median cingulate and paracingulate. In addition, PKD-M showed decreased nodal centralities, relative to HC and to PKD-M, in bilateral supplementary motor area, left angular gyrus, right caudate nucleus, bilateral pallidum, and right superior temporal gyri (Table 3, Figure 1).

3.4 Structural Connections

In the NBS analysis, compared with HC, the PKD-N showed a significant subnetwork with 4 nodes and 4 connections and the PKD-M a significant subnetwork with 12 nodes and 19 connections. Compared with PKD-N, PKD-M showed a significant subnetwork with 7 nodes and 12 connections. All connections in these subnetworks were decreased and this was more pronounced in PKD-M. These nodes involved supplementary motor area, basal ganglia, thalamus, angular gyrus, posterior cingulate gyrus, and the temporal lobes (Figure 2).

3.5 Relationships between topological metrics and clinical variables

Using age, gender and years of education as covariates in partial correlation analysis, we detected no significant correlations between network parameters and age of onset or disease duration in either group.

3.6 Single-subject classification of patients with or without PRRT2 mutation

Using gray matter structural network metrics, the mean balanced accuracy of classification of patients with and without PRRT2 mutations was 74.3%, with sensitivity 80.0% and specificity 68.7% ($p < 0.001$).

4 DISCUSSION

By investigating single-subject gray matter structural networks of PKD patients with or without PRRT2 mutation, compared to healthy controls, we have demonstrated for the first time PRRT2-related abnormalities in gray matter structural networks in PKD. At the global network level, only patients with PRRT2 mutation showed an increase in characteristic path length and a decrease in global efficiency and local efficiency. At the level of nodal topology, both PKD groups showed decreased nodal centralities and structural connections in right postcentral gyrus, right angular, bilateral thalamus, and left median cingulate and paracingulate gyri. Patients with PRRT2 mutations showed additional decreased nodal centralities and structural connections in bilateral supplementary motor area, left angular gyrus, right caudate nucleus, and

bilateral pallidum, and right superior temporal gyrus..

Although the genotype–phenotype relationship has not been fully clarified in PKD, many studies find a strong relation between PRRT2 mutation and clinical presentation. Compared to patients without the mutation, PRRT2 mutation patients have an earlier age at onset (as in our sample), and are more likely to have a family history (as in our sample); their attacks last longer (as in our sample) and occur more frequently, more often combine dystonia and chorea, and are more often bilateral; therapeutically, carbamazepine is more effective (Huang et al., 2020; Huang et al., 2015; H. F. Li et al., 2013; McGovern, Roze, & Counihan, 2018; Tan et al., 2014).

The small-world topology of normal brain networks reflects an optimal balance between local segregation and global integration of information (Deco, Tononi, Boly, & Kringelbach, 2015). Graph-based brain network analyses provides a robust way to quantify such information integration (reflected by Lp, λ, and Eglob) and segregation (reflected by Cp, γ, and Eloc) (Rubinov & Sporns, 2010; Suo et al., 2018). Both PKD patients and HCs showed high Cp and low Lp, confirming that their gray matter structural networks have a small-world topology. However, relative to PKD-N and HC, PKD-M showed higher Lp and lower Eloc and Eglob, implying a shift to “weaker small-worldness” with less efficient information processing and transfer. This phenomenon has been noted in white matter structural networks (L. Li et al., 2020) and in gray matter morphological networks (X. Li et al., 2021) in a study which did not distinguish the subtypes. Although the physiological meaning of the structural covariance network is not fully understood, it is affected by heredity and environment (Alexander-Bloch et al., 2013; Hawrylycz et al., 2012; Kong et al., 2014). PRRT2 is highly expressed in the central nervous system and involved in brain development and synapse formation, and the PRRT2 expression pattern in the developing mouse brain corresponds with the age-dependent development pattern of PKD (J. L. Wang et al., 2011). All this seems to point to PRRT2 mutation as a key factor affecting the topological organization of the gray matter structural covariance network in patients with PKD.

The nodal network analysis helps identify specifically altered brain regions and networks. A key system is the cortical-basal ganglia-thalamo-cortical circuit (CBTC), important in the control of movement. CBTC dysfunction has been hypothesized to play a role in hyperkinetic symptoms, and specifically in PKD [*reference?]*. The CBTC loop originates from the motor cortices including the primary motor cortex, supplementary motor area, and lateral premotor cortex; it projects to the somatomotor region of the basal ganglia, then to the thalamus, which in turn projects back to the motor cortex (Breakefield et al., 2008; Tekin & Cummings, 2002). We found abnormal nodal topological organization and structural connections throughout the motor loop of the CBTC; in bilateral thalamus, right caudate nucleus, bilateral pallidum and bilateral supplementary motor area. The. alteration of nodal properties in right caudate nucleus, bilateral pallidum and bilateral supplementary motor only occurred in PRRT2-mutated patients, suggesting these are PRRT2-related features. PRRT2 is highly expressed in the cortical layers of the cerebral cortex and basal ganglia, involved in brain development and synapse formation (W. J. Chen et al., 2011; Ebrahimi-Fakhari et al., 2015). However, the relationship between the biological changes and alterations in the brain network need to be further studied.

We also found abnormal nodal topological organizations and structural connections in right posterior cingulate gyrus, bilateral angular gyrus, left superior temporal gyrus, and left median cingulate and paracingulate gyri in patients with PRRT2 mutations. Those regions have been considered as key components of the default-mode network (DMN) (Buckner, Andrews-Hanna, & Schacter, 2008; Raichle, 2015). Although median cingulate and paracingulate gyri abnormalities are not commonly reported in PKD, DMN abnormalities have been described and are possibly related to abnormal emotional processing (X. Li et al., 2021; Y. Zhang et al., 2020), which could explain why PKD symptoms depend on the internal emotional state: anxiety and stress lower the threshold for attacks and startle can also trigger the attack. However, nodal characteristics in these regions were altered in both PKD patient groups, so DMN involvement may be a more general phenomenon in PKD.

Consistent with our second hypothesis, the accuracy of classification of PKD-N *vs* PKD-M using gray matter structural network matrices was quite high at 74.3%. Network imaging biomarkers which can capture brain network structure and the phenotypic role of known subsystems have the potential to improve diagnosis of neuropsychiatric diseases (Schindlbeck & Eidelberg, 2018; Wen et al., 2017). A recent study in schizophrenia suggested that connectome-wide matrices had greater diagnostic value than graph-based metrics or preprocessed whole-brain image data (Lei et al., 2020). Moreover, our earlier study showed that gray matter morphological network matrices can identify PKD from controls with a high accuracy (X. Li et al., 2021). Our results raise the hope that brain networks based on structural MRI might similarly yield a practical marker to distinguish patients with or without PRRT2 mutation.

Our study has some limitations. First, some patients were treated with antiepileptic drugs, as often recommended (Huang et al., 2015), so potential confounding effects of medication on brain structural networks cannot be ruled out. Second, the prevalence of PRRT2 mutation in patients with PKD ranges from 27% to 65%, indicating that PRRT2–negative cases might have additional culprit genes (Tian et al., 2018), which should also be considered in future studies. Third, although the spatial resolution of our data is comparable with that used in previous gray matter network analyses (Niu et al., 2018), higher resolution data should be acquired in the future to increase precision .

In conclusion, this study revealed for the first time that PKD patients with PRRT2 mutations featured (globally) a “weaker small-worldness” gray matter network organization, and (locally) more extensive regional disturbance and structural connections in CBTC, suggesting that these are PRRT2-related network traits and that PRRT2 mutations affect PKD possibly by modulating such brain networks. These finding may help to understand the PRRT2-related neural circuitry involved in PKD.

Acknowledgements

This study was supported by the National Natural Science Foundation
(Grant Nos. 81621003, 81820108018, 8202780056, and 81761128023), the Program

for Changjiang Scholars and Innovative Research Team in University (PCSIRT, grant IRT16R52) of China.

Conflict of interest

All authors declare no competing interests.

Data availability statement

The datasets generated for this study are available on request to the corresponding author.

References

Alexander-Bloch, A., Giedd, J. N., & Bullmore, E. (2013). Imaging structural co-variance between human brain regions. *Nat Rev Neurosci, 14*(5), 322-336. doi:10.1038/nrn3465

Batalle, D., Muñoz-Moreno, E., Figueras, F., Bargallo, N., Eixarch, E., & Gratacos, E. (2013). Normalization of similarity-based individual brain networks from gray matter MRI and its association with neurodevelopment in infants with intrauterine growth restriction. *Neuroimage, 83*, 901-911. doi:10.1016/j.neuroimage.2013.07.045

Benjamini, Y., Drai, D., Elmer, G., Kafkafi, N., & Golani, I. (2001). Controlling the false discovery rate in behavior genetics research. *Behav Brain Res, 125*(1-2), 279-284. doi:10.1016/s0166-4328(01)00297-2

Bhatia, K. P. (2011). Paroxysmal dyskinesias. *Mov Disord, 26*(6), 1157-1165. doi:10.1002/mds.23765

Breakefield, X. O., Blood, A. J., Li, Y., Hallett, M., Hanson, P. I., & Standaert, D. G. (2008). The pathophysiological basis of dystonias. *Nat Rev Neurosci, 9*(3), 222-234. doi:10.1038/nrn2337

Bruno, M. K., Hallett, M., Gwinn-Hardy, K., Sorensen, B., Considine, E., Tucker, S., . . . Ptacek, L. J. (2004). Clinical evaluation of idiopathic paroxysmal kinesigenic dyskinesia: new diagnostic criteria. *Neurology, 63*(12), 2280-2287. doi:10.1212/01.wnl.0000147298.05983.50

Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci, 1124*, 1-38. doi:10.1196/annals.1440.011

Chang, C. C., & Lin, C. J. (2011). LIBSVM: A library for support vector machines. *ACM Transactions on Intelligent Systems and Technology*.

Chen, T., Kendrick, K. M., Wang, J., Wu, M., Li, K., Huang, X., . . . Gong, Q. (2017). Anomalous single-subject based morphological cortical networks in drug-naive, first-episode major depressive disorder. *Hum Brain Mapp, 38*(5), 2482-2494. doi:10.1002/hbm.23534

Chen, W. J., Lin, Y., Xiong, Z. Q., Wei, W., Ni, W., Tan, G. H., . . . Wu, Z. Y. (2011). Exome sequencing identifies truncating mutations in PRRT2 that cause paroxysmal kinesigenic dyskinesia. *Nat Genet, 43*(12), 1252-1255. doi:10.1038/ng.1008

Deco, G., Tononi, G., Boly, M., & Kringelbach, M. L. (2015). Rethinking segregation and integration: contributions of whole-brain modelling. *Nat Rev Neurosci, 16*(7), 430-439. doi:10.1038/nrn3963

Donahue, C. J., Sotiropoulos, S. N., Jbabdi, S., Hernandez-Fernandez, M., Behrens, T. E., Dyrby, T. B., . . . Glasser, M. F. (2016). Using Diffusion Tractography to Predict Cortical Connection Strength and Distance: A Quantitative Comparison with Tracers in the Monkey. *J Neurosci, 36*(25), 6758-6770. doi:10.1523/jneurosci.0493-16.2016

Ebrahimi-Fakhari, D., Moufawad El Achkar, C., & Klein, C. (2018). PRRT2-Associated Paroxysmal Movement Disorders. In M. P. Adam, H. H. Ardinger, R. A. Pagon, S. E. Wallace, L. J. H. Bean, G. Mirzaa, & A. Amemiya (Eds.), *GeneReviews(®)*. Seattle (WA): University of Washington, Seattle

Ebrahimi-Fakhari, D., Saffari, A., Westenberger, A., & Klein, C. (2015). The evolving spectrum of PRRT2-associated paroxysmal diseases. *Brain, 138*(Pt 12), 3476-3495. doi:10.1093/brain/awv317

Elman, J. A., Panizzon, M. S., Hagler, D. J., Jr., Fennema-Notestine, C., Eyler, L. T., Gillespie, N. A., . . . Kremen, W. S. (2017). Genetic and environmental influences on cortical mean diffusivity. *Neuroimage, 146*, 90-99. doi:10.1016/j.neuroimage.2016.11.032

Golland, P., & Fischl, B. (2003). Permutation Tests for Classification: Towards Statistical Significance in Image-Based Studies. *Inf Process Med Imaging, 18*, 330-341.

Hawrylycz, M. J., Lein, E. S., Guillozet-Bongaarts, A. L., Shen, E. H., Ng, L., Miller, J. A., . . . Jones, A. R. (2012). An anatomically comprehensive atlas of the adult human brain transcriptome. *Nature, 489*(7416), 391-399. doi:10.1038/nature11405

He, Y., Dagher, A., Chen, Z., Charil, A., Zijdenbos, A., Worsley, K., & Evans, A. (2009). Impaired small-world efficiency in structural cortical networks in multiple sclerosis associated with white matter lesion load. *Brain, 132*(Pt 12), 3366-3379. doi:10.1093/brain/awp089

Huang, X. J., Wang, S. G., Guo, X. N., Tian, W. T., Zhan, F. X., Zhu, Z. Y., . . . Cao, L. (2020). The Phenotypic and Genetic Spectrum of Paroxysmal Kinesigenic Dyskinesia in China. *Mov Disord, 35*(8), 1428-1437. doi:10.1002/mds.28061

Huang, X. J., Wang, T., Wang, J. L., Liu, X. L., Che, X. Q., Li, J., . . . Chen, S. D. (2015). Paroxysmal kinesigenic dyskinesia: Clinical and genetic analyses of 110 patients. *Neurology, 85*(18), 1546-1553. doi:10.1212/wnl.0000000000002079

Iturria-Medina, Y., Canales-Rodríguez, E. J., Melie-García, L., Valdés-Hernández, P. A., Martínez-Montes, E., Alemán-Gómez, Y., & Sánchez-Bornot, J. M. (2007). Characterizing brain anatomical connections using diffusion weighted MRI and graph theory. *Neuroimage, 36*(3), 645-660. doi:10.1016/j.neuroimage.2007.02.012

Kim, J. H., Kim, D. W., Kim, J. B., Suh, S. I., & Koh, S. B. (2015). Thalamic involvement in paroxysmal kinesigenic dyskinesia: a combined structural and diffusion tensor MRI analysis. *Hum Brain Mapp, 36*(4), 1429-1441. doi:10.1002/hbm.22713

Kong, X. Z., Wang, X., Huang, L., Pu, Y., Yang, Z., Dang, X., . . . Liu, J. (2014). Measuring individual morphological relationship of cortical regions. *J Neurosci Methods, 237*, 103-107. doi:10.1016/j.jneumeth.2014.09.003

Lee, H. Y., Huang, Y., Bruneau, N., Roll, P., Roberson, E. D., Hermann, M., . . . Ptáček, L. J. (2012). Mutations in the gene PRRT2 cause paroxysmal kinesigenic dyskinesia with infantile convulsions. *Cell Rep, 1*(1), 2-12. doi:10.1016/j.celrep.2011.11.001

Lei, D., Pinaya, W. H. L., van Amelsvoort, T., Marcelis, M., Donohoe, G., Mothersill, D. O., . . . Mechelli, A. (2020). Detecting schizophrenia at the level of the individual: relative diagnostic value of whole-brain images, connectome-wide functional connectivity and graph-based metrics. *Psychol Med, 50*(11), 1852-1861. doi:10.1017/s0033291719001934

Li, H. F., Chen, W. J., Ni, W., Wang, K. Y., Liu, G. L., Wang, N., . . . Wu, Z. Y. (2013). PRRT2 mutation correlated with phenotype of paroxysmal kinesigenic dyskinesia and drug response. *Neurology, 80*(16), 1534-1535. doi:10.1212/WNL.0b013e31828cf7e1

Li, J., Zhu, X., Wang, X., Sun, W., Feng, B., Du, T., . . . Liu, Y. (2012). Targeted genomic sequencing identifies PRRT2 mutations as a cause of paroxysmal kinesigenic choreoathetosis. *J Med Genet, 49*(2), 76-78. doi:10.1136/jmedgenet-2011-100635

Li, L., Lei, D., Suo, X., Li, X., Yang, C., Yang, T., . . . Gong, Q. (2020). Brain structural connectome in relation to PRRT2 mutations in paroxysmal kinesigenic dyskinesia. *Hum Brain Mapp, 41*(14), 3855-3866. doi:10.1002/hbm.25091

Li, X., Lei, D., Niu, R., Li, L., Suo, X., Li, W., . . . Gong, Q. (2021). Disruption of gray matter morphological networks in patients with paroxysmal kinesigenic dyskinesia. *Hum Brain Mapp, 42*(2), 398-411. doi:10.1002/hbm.25230

Liu, Y. T., Nian, F. S., Chou, W. J., Tai, C. Y., Kwan, S. Y., Chen, C., . . . Tsai, J. W. (2016). PRRT2 mutations lead to neuronal dysfunction and neurodevelopmental defects. *Oncotarget, 7*(26), 39184-39196. doi:10.18632/oncotarget.9258

Long, Z., Xu, Q., Miao, H. H., Yu, Y., Ding, M. P., Chen, H., . . . Liao, W. (2017). Thalamocortical dysconnectivity in paroxysmal kinesigenic dyskinesia: Combining functional magnetic resonance imaging and diffusion tensor

imaging. *Mov Disord, 32*(4), 592-600. doi:10.1002/mds.26905

Luo, C., Chen, Y., Song, W., Chen, Q., Gong, Q., & Shang, H. F. (2013). Altered intrinsic brain activity in patients with paroxysmal kinesigenic dyskinesia by PRRT2 mutation: altered brain activity by PRRT2 mutation. *Neurol Sci, 34*(11), 1925-1931. doi:10.1007/s10072-013-1408-7

McGovern, E. M., Roze, E., & Counihan, T. J. (2018). The expanding spectrum of paroxysmal movement disorders: update from clinical features to therapeutics. *Curr Opin Neurol, 31*(4), 491-497. doi:10.1097/wco.0000000000000576

Méneret, A., Grabli, D., Depienne, C., Gaudebout, C., Picard, F., Dürr, A., . . . Roze, E. (2012). PRRT2 mutations: a major cause of paroxysmal kinesigenic dyskinesia in the European population. *Neurology, 79*(2), 170-174. doi:10.1212/WNL.0b013e31825f06c3

Niu, R., Lei, D., Chen, F., Chen, Y., Suo, X., Li, L., . . . Gong, Q. (2018). Disrupted grey matter network morphology in pediatric posttraumatic stress disorder. *Neuroimage Clin, 18*, 943-951. doi:10.1016/j.nicl.2018.03.030

Novellino, F., López, M. E., Vaccaro, M. G., Miguel, Y., Delgado, M. L., & Maestu, F. (2019). Association Between Hippocampus, Thalamus, and Caudate in Mild Cognitive Impairment APOEε4 Carriers: A Structural Covariance MRI Study. *Front Neurol, 10*, 1303. doi:10.3389/fneur.2019.01303

Pedregosa, F., Varoquaux, G., Gramfort, A., Michel, V., Thirion, B., Grisel, O., . . . Louppe, G. (2012). Scikit-learn: Machine Learning in Python.

Raichle, M. E. (2015). The brain's default mode network. *Annu Rev Neurosci, 38*, 433-447. doi:10.1146/annurev-neuro-071013-014030

Richmond, S., Johnson, K. A., Seal, M. L., Allen, N. B., & Whittle, S. (2016). Development of brain networks and relevance of environmental and genetic factors: A systematic review. *Neurosci Biobehav Rev, 71*, 215-239. doi:10.1016/j.neubiorev.2016.08.024

Rubinov, M., & Sporns, O. (2010). Complex network measures of brain connectivity: uses and interpretations. *Neuroimage, 52*(3), 1059-1069. doi:10.1016/j.neuroimage.2009.10.003

Schindlbeck, K. A., & Eidelberg, D. (2018). Network imaging biomarkers: insights and clinical applications in Parkinson's disease. *Lancet Neurol, 17*(7), 629-640. doi:10.1016/s1474-4422(18)30169-8

Suo, X. S., Lei, D. L., Li, L. L., Li, W. L., Dai, J. D., Wang, S. W., . . . Gong, Q. G. (2018). Psychoradiological patterns of small-world properties and a systematic review of connectome studies of patients with 6 major psychiatric disorders. *J Psychiatry Neurosci, 43*(6), 427. doi:10.1503/jpn.170214

Tan, L. C., Methawasin, K., Teng, E. W., Ng, A. R., Seah, S. H., Au, W. L., . . . Tan, E. K. (2014). Clinico-genetic comparisons of paroxysmal kinesigenic dyskinesia patients with and without PRRT2 mutations. *Eur J Neurol, 21*(4), 674-678. doi:10.1111/ene.12142

Tekin, S., & Cummings, J. L. (2002). Frontal-subcortical neuronal circuits and clinical neuropsychiatry: an update. *J Psychosom Res, 53*(2), 647-654. doi:10.1016/s0022-3999(02)00428-2

Tian, W. T., Huang, X. J., Mao, X., Liu, Q., Liu, X. L., Zeng, S., . . . Cao, L. (2018). Proline-rich transmembrane protein 2-negative paroxysmal kinesigenic dyskinesia: Clinical and genetic analyses of 163 patients. *Mov Disord, 33*(3), 459-467. doi:10.1002/mds.27274

Tijms, B. M., Seriès, P., Willshaw, D. J., & Lawrie, S. M. (2012). Similarity-based extraction of individual networks from gray matter MRI scans. *Cereb Cortex, 22*(7), 1530-1541. doi:10.1093/cercor/bhr221

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., . . . Joliot, M. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage, 15*(1), 273-289. doi:10.1006/nimg.2001.0978

Valente, P., Castroflorio, E., Rossi, P., Fadda, M., Sterlini, B., Cervigni, R. I., . . . Benfenati, F. (2016). PRRT2 Is a Key Component of the Ca(2+)-Dependent Neurotransmitter Release Machinery. *Cell Rep, 15*(1), 117-131. doi:10.1016/j.celrep.2016.03.005

Valtorta, F., Benfenati, F., Zara, F., & Meldolesi, J. (2016). PRRT2: from Paroxysmal Disorders to Regulation of Synaptic Function. *Trends Neurosci, 39*(10), 668-679. doi:10.1016/j.tins.2016.08.005

van Wijk, B. C., Stam, C. J., & Daffertshofer, A. (2010). Comparing brain networks of different size and connectivity density using graph theory. *PLoS One, 5*(10), e13701. doi:10.1371/journal.pone.0013701

Wang, J., Wang, X., Xia, M., Liao, X., Evans, A., & He, Y. (2015). GRETNA: a graph theoretical network analysis toolbox for imaging connectomics. *Front Hum Neurosci, 9*, 386. doi:10.3389/fnhum.2015.00386

Wang, J. L., Cao, L., Li, X. H., Hu, Z. M., Li, J. D., Zhang, J. G., . . . Tang, B. S. (2011). Identification of PRRT2 as the causative gene of paroxysmal kinesigenic dyskinesias. *Brain, 134*(Pt 12), 3493-3501. doi:10.1093/brain/awr289

Watts, D. J., & Strogatz, S. H. (1998). Collective dynamics of 'small-world' networks. *Nature, 393*(6684), 440-442. doi:10.1038/30918

Weese, J., Rsch, P., Netsch, T., Blaffert, T., & Quist, M. (1999). Gray-Value Based Registration of CT and MR Images by Maximization of Local Correlation. *Medical Image Computing and Computer-Assisted Intervention-MICCAI'99, 1679*, 656-663.

Wen, H., Liu, Y., Rekik, I., Wang, S., Zhang, J., Zhang, Y., . . . He, H. (2017). Disrupted topological organization of structural networks revealed by probabilistic diffusion tractography in Tourette syndrome children. *Hum Brain Mapp, 38*(8), 3988-4008. doi:10.1002/hbm.23643

Zalesky, A., Fornito, A., & Bullmore, E. T. (2010). Network-based statistic: identifying differences in brain networks. *Neuroimage, 53*(4), 1197-1207. doi:10.1016/j.neuroimage.2010.06.041

Zhang, J., Wang, J., Wu, Q., Kuang, W., Huang, X., He, Y., & Gong, Q. (2011). Disrupted brain connectivity networks in drug-naive, first-episode major depressive disorder. *Biol Psychiatry, 70*(4), 334-342. doi:10.1016/j.biopsych.2011.05.018

Zhang, W., Lei, D., Keedy, S. K., Ivleva, E. I., Eum, S., Yao, L., . . . Sweeney, J. A. (2020). Brain gray matter network organization in psychotic disorders. *Neuropsychopharmacology, 45*(4), 666-674. doi:10.1038/s41386-019-0586-2

Zhang, Y., Ren, J., Qin, Y., Yang, C., Zhang, T., Gong, Q., . . . Zhou, D. (2020). Altered topological organization of functional brain networks in drug-naive patients with paroxysmal kinesigenic dyskinesia. *J Neurol Sci, 411*, 116702. doi:10.1016/j.jns.2020.116702

Zhao, Y., Niu, R., Lei, D., Shah, C., Xiao, Y., Zhang, W., . . . Gong, Q. (2020). Aberrant Gray Matter Networks in Non-comorbid Medication-Naive Patients With Major Depressive Disorder and Those With Social Anxiety Disorder. *Front Hum Neurosci, 14*, 172. doi:10.3389/fnhum.2020.00172

Zhou, B., Chen, Q., Zhang, Q., Chen, L., Gong, Q., Shang, H., . . . Zhou, D. (2010). Hyperactive putamen in patients with paroxysmal kinesigenic choreoathetosis: a resting-state functional magnetic resonance imaging study. *Mov Disord, 25*(9), 1226-1231. doi:10.1002/mds.22967