



Altered Functional Brain Connectomes between Sporadic and Familial Parkinson's Patients

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Received: 11 July 2017

Accepted: 19 October 2017

Published: 06 November 2017

Citation:

Tang Y, Xiao X, Xie H, Wan C-m, Meng L, Liu Z-h, Liao W-h, Tang B-s and Guo J-f (2017) Altered Functional Brain Connectomes between Sporadic and Familial Parkinson's Patients. *Front. Neuroanat.* 11:99. doi: 10.3389/fnana.2017.00099

Familial Parkinson's disease (PD) is often caused by mutation of a certain gene, while sporadic PD is associated with variants of genes which can influence the susceptibility to PD. The goal of this study was to investigate the difference between the two forms of PD in terms of brain abnormalities using resting-state functional MRI and graph theory. Thirty-one familial PD patients and 36 sporadic PD patients underwent resting-state functional MRI scanning. Frequency-dependent functional connectivity was calculated for each subject using wavelet-based correlations of BOLD signal over 246 brain regions from Brainnetome Atlas. Graph theoretical analysis was then performed to analyze the topology of the functional network, and functional connectome differences were identified with a network-based statistical approach. Our results revealed a frequency-specific (0.016 and 0.031 Hz) connectome difference between familial and sporadic forms of PD, as indicated by an increase in assortativity and decrease in the nodal strength in the left medial amygdala of the familial PD group. In addition, the familial PD patients also showed a distinctive functional network between the left medial amygdala and regions related to retrieval of motion information. The present study indicates that the medial amygdala might be most vulnerable to both sporadic and familial PD. Our findings provide some new insights into disrupted resting-state functional connectomes between sporadic PD and familial PD.

Keywords: functional brain connectome, sporadic PD, familial PD, assortativity, small-worldness

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disease with symptoms such as resting tremor, rigidity, akinesia and postural instability as shown by Parkinson (2002). It was reported by Hauser and Hastings (2013) that in about 95% of PD cases, there is no apparent genetic linkage (sporadic PD), while for the rest cases, the disease is inherited and have monogenic forms (familial PD). Familial PD is often caused by mutation of a certain gene, while sporadic PD is associated with variants of genes which can influence the susceptibility of developing PD (Guo et al., 2008; Ciceri et al., 2017). Thompson et al. (2001) has reported that genes affecting the development and function

of brain that mediated the expression of such diverse behavioral, cognitive and perceptual phenomena. Dujardin et al. (2001) provided evidence that sporadic PD and familial PD differ in terms of cognitive impairment that deficits of explicit memory recall were only observed in patients with sporadic PD. Despite the recent discovery of the mutation patterns, the two forms of PD are difficult to distinguish clinically and pathologically (Chai and Lim, 2013), and the underlying disease-related neural mechanism of different forms of PD remains elusive. As suggested by Palop et al. (2006) that neurodegenerative diseases may lead to network dysfunction, we decide to explore the brain's potential functional network difference between sporadic PD and familial PD to further our understanding of the pathogenic mechanism difference between the two.

Resting functional Magnetic Resonance Imaging (R-fMRI) measures the intrinsic or spontaneous neuronal activity of the brain (Fox and Raichle, 2007) and has shown PD-related breakdowns in functional brain synchronization (Hacker et al., 2012; Tessitore et al., 2012). Recent developments in the quantitative analysis of complex networks using graph theory, have enabled the exploration of the network architectures of brain system (Sporns et al., 2005). Moreover, many studies have suggested the potential link between various brain diseases and altered topological patterns in the functional connectivity (Lynall et al., 2010; Rubinov and Sporns, 2010; Sanz-Arigita et al., 2010). Graph theory has also been applied to investigate the abnormal functional brain network in PD patients. For example, Göttlich et al. (2013) and Fang et al. (2017) both found PD exhibited disruptive visual networks in early disease stage; Luo et al. (2015) found the decreases in local efficiency and local clustering coefficient in the weighted brain network of drug-naive PD patients. The above-mentioned studies have shed some light into the abnormal connectome associated with PD but the differences in terms of the topological architectures of brain connectome present in sporadic PD and familial PD remain largely unknown.

The BOLD power spectrum exhibits scale-free feature. As suggested by Baria et al. (2011), the lower frequency band exhibits the higher magnitude including prefrontal, parietal, and occipital cortices, especially within several default-mode regions; the higher frequency band exhibits less power, and localizes more within subcortical structures (e.g., thalamus and basal ganglia). Independent frequency bands are generated by distinct oscillators with specific properties and physiological functions highlighting the significance of frequency information in neural oscillations (Buzsáki and Draguhn, 2004; Zuo et al., 2010). In fact, the frequency-dependent intrinsic activity pattern altered by diseases have been widely reported, e.g., Alzheimer's disease (Li et al., 2017), PD (Zhang et al. (2015), and schizophrenia (Yu et al., 2014). More recently, the wavelet-based frequency analysis (Percival and Walden, 2006) has been applied in conjunction with resting-state functional connectivity (RSFC) to further the understanding of the pathophysiology of various diseases including mild cognitive impairment (Wang et al., 2013), antisocial personality disorder (Tang et al., 2016), and Alzheimer's Disease (Supekar et al., 2008). Skidmore et al. (2011) and Zhang et al. (2015) both discovered that in PD patients, the information translation in the functional brain network was

disrupted within the wavelet scale 2 (i.e., 0.063–0.125 Hz), which could be related to acute dopamine depletion. However, Dujardin et al. (2001) emphasized the contribution of nondopaminergic loops to development of sporadic PD. Along those lines, we followed an earlier study investigating PD-related spontaneous brain activity (Zhang et al., 2015) and decomposed RSFC into four wavelet scales (scale 1, 0.125–0.250 Hz; scale 2, 0.063–0.125 Hz; scale 3, 0.031–0.063 Hz; and scale 4, 0.016–0.031 Hz). We aimed to investigate frequency-dependent difference in the global and local functional network topology alternation between sporadic and familial PD.

MATERIALS AND METHODS

Ethics Statement

This study was performed in accordance with the recommendations of the ethics committee of Central South University (Changsha, China) with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the ethics committee of Central South University (Changsha, China).

Subjects

The PD patients were diagnosed based on their history and a neurologic examination conducted by a fellowship-trained movement disorders specialist. The clinical diagnosis of PD was made based on the UK Parkinson's Disease Society Brain Bank (UKPDBB) criteria (Hughes et al., 1992, 2001) by two or more experienced neurologists. Each patient with definite PD and accompanying family members were interviewed for Parkinson's disease, Parkinson's disease-like symptoms and any other central nervous system (CNS) disorder among the first or second degree relatives. When a secondary case of PD was found in a family, this affected person was examined by a neurologist based on UKPDBB criteria to make a definitive diagnosis of Parkinson's disease. If no other occurrence of PD was identified in the family after thorough investigation, the case was considered as sporadic. Relatives reported to be unaffected by PD or any other CNS disorder were not examined, as Maraganore and colleagues found no false negatives among relatives reported as normal (Maraganore et al., 1991).

Sixty-seven PD patients were recruited for the study. The patients consisted of 31 familial PD patients with at least one relative of the first or the second degree also identified as PD, according to the criteria previously described. The exclusion criteria included moderate-to-severe head tremor, other neurological diseases (e.g., severe head trauma or stroke), and other general exclusion criteria for MRI scanning (e.g., claustrophobia, wearing pace-maker, and implanted metal parts).

All patients were studied in the off-medication state after all antiparkinsonian drugs had been withheld. Before the patients were scanned, they underwent a series of neurological examinations and neuropsychological testing including assessments with the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn and Elton, 1987), the Hoehn and Yahr (H-Y) stage (Hoehn and Yahr, 1967; Goetz, 2003), the Mini-Mental

Status (MMSE) (Folstein et al., 1975) and Hamilton Depression Scale (HAMD) (Hamilton, 1960).

Image Acquisition

All scans were performed using a 3T GE Signa MR scanner (General Electric, Fairfield, CT, USA) in the Department of Radiology of Xiangya Hospital of Central South University. Earplugs were used to reduce scanner noise, and head motion was restricted via a foam pillow and extendable padded head clamps. The participants were instructed to rest with their eyes closed, relax and lie still. Functional scans were acquired using a gradient echo EPI (GE-EPI) sequence with the following parameters: $TR = 2,000$ ms, $TE = 30$ ms, slice thickness = 4.0 mm, flip angle = 90° , slice number = 32 and voxel size = $3.44 \times 3.44 \times 4.60$ mm. One hundred eighty image volumes were acquired for each participant over the course of 6 min.

Data Preprocessing

Data preprocessing was carried out using SPM8 (www.fil.ion.ucl.ac.uk/spm/); and DPARSF (Chao-Gan and Yu-Feng, 2010) (<http://www.restfmri.net>). The first 10 volumes were discarded to achieve scanner equilibrium. The remaining 170 images underwent slice timing and motion correction, and no subjects were found with head motion more than 1.5 mm of translation or greater than 1.5° of rotation in any of the x, y, or z axis. Next, the images were spatially normalized to Montreal Neurological Institute (MNI) space with the voxel size of $3 \times 3 \times 3$ mm. No spatial smoothing was performed to avoid degradation of diagnosticity (Kriegeskorte et al., 2006). The resulting volumes were detrended and temporally filtered using a high-pass filter (cut-off frequency = 0.01 Hz). Finally, the nuisance signal regression was performed with six rigid-body motion parameters, white matter and cerebrospinal fluid signal (Desjardins et al., 2001; Fox et al., 2009). Because of the controversy of global signal regression (GSR) during the preprocessing which may create anti-correlated patterns (Fox et al., 2009; Murphy et al., 2009), GSR was not performed following previous studies of wavelet-based functional brain networks (Di Martino et al., 2009; Lynall et al., 2010; Wang et al., 2013). Functional connectivity was then computed on the residual signal using wavelet-based frequency analysis.

Network Construction

The processed images were parcellated into 246 regions of interests (ROIs) that included 210 cortical and 36 subcortical subregions according to the Brainnetome atlas (Fan et al., 2016). Brainnetome atlas is a fine-grained, cross-validated atlas correlating brain anatomy with psychological and cognitive functions. In the following graphical analysis, each ROI represented a node in the functional brain network. The mean time series were computed by averaging the BOLD signal of all voxels within each ROI.

Wavelet-based frequency analysis has been brought up to further the understanding of the pathophysiology of various diseases (Percival and Walden, 2006; Tang et al., 2016). In order to measure the intrinsic pattern of specific frequency bands, discrete wavelet transform was applied to compute the interregional frequency-dependent RSFC, which reflects the

functional associations between brain regions evoked by activities of different frequency intervals and wavelet scales (Maxim et al., 2005; Achard et al., 2006). Here, functional connectivity was estimated in the first four wavelet scales (scale 1, 0.125–0.250 Hz; scale 2, 0.063–0.125 Hz; scale 3, 0.031–0.063 Hz; and scale 4, 0.016–0.031 Hz) as in Zhang et al. (2015). The correlation matrices were then converted into adjacency matrices $A_{ij} = [a_{ij}]$. To control a family-wise significance level of 0.05 of 0.05, Bonferroni adjusted p -value threshold was computed as 0.05 divided by the total number of links ($246 \times 245/2 = 30,135$) = 1.659×10^{-6} . The entry a_{ij} was the Pearson's correlation coefficient if the Bonferroni adjusted p -value was below the statistical threshold ($p < 0.05$, Bonferroni-corrected) and was set to 0 otherwise, as shown in Equation (1).

$$a_{ij} = \begin{cases} \text{Pearson's correlation coefficient} & \text{if } p < 0.05, \text{ Bonferroni-corrected} \\ 0 & \text{otherwise} \end{cases} \quad (1)$$

Considering the ambiguous physiological meaning of negative correlations, negative connections were also set to zero.

Network Analysis

To characterize the topological organizations of weighted functional networks, the following graph theoretical measures were evaluated: clustering coefficient, characteristic path length, small-worldness, assortativity, and nodal strength. The clustering coefficient (C_p) was defined as the average of the clustering coefficients over all nodes reflecting the possibility that the neighbors of a vertex would also be connected. C_p is between the range of 0 and 1, and is equal to 1 if and only if the network is fully connected. The characteristic path length L_p is the average of the length of the shortest path between the all pairs of vertices, and it is a measure of the overall routing efficiency of the network. To assess the small-worldness of the constructed functional networks, we simulated 1,000 random networks via random rewiring using the same number of nodes, mean degree and degree distribution of the real network, and calculated the mean clustering coefficient C_p^{rand} , and the mean characteristic path length L_p^{rand} of the 1,000 simulated random networks. A network with small-world topology can be characterized as follows: $\gamma = \frac{C_p}{C_p^{\text{rand}}} > 1$, $\lambda = \frac{L_p}{L_p^{\text{rand}}} \approx 1$ and $\sigma = \frac{\gamma}{\lambda} > 1$.

The resilience of brain systems could be impaired by various diseases. To assess the resilience of the brain network, the assortativities of four wavelet scales were computed, using Equation (2) (Newman, 2002; Achard et al., 2006):

$$r = \frac{\frac{1}{T} \sum_{j>i} k_i k_j a_{ij}}{\left[\frac{1}{T} \sum_{j>i} (k_i^2 + k_j^2) a_{ij} - \left[\frac{1}{T} \sum_{j>i} \frac{1}{2} (k_i + k_j) a_{ij} \right]^2 \right]} \quad (2)$$

where T is the number of the links in the network, a_{ij} is the corresponding element of the adjacency matrix between nodes i and j , and k_i is the degree of node i . In general, r lies between -1 and 1. An assortative network has positive assortativity, which indicates a network with more mutually coupled hub nodes, whereas $r < 0$ implies a disassortative network in where high-degree hub nodes are unlikely to be inter-linked (Barzegaran et al., 2012).

Although many nodal metrics could be used to characterize regional centrality (Zuo et al., 2012), we employed the nodal strength (i.e., the weighted degree centrality) because of its high test-retest reliability (Wang et al., 2011). The nodal strength of a given node in a network is defined in Equation (3) as the sum of all edge weights a_{ij} between a given node and all other nodes in the network:

$$k_i = \sum_{j \in N} a_{ij} \quad (3)$$

Statistical Analysis

Group differences in the topological architectures (global measures) were characterized using nonparametric permutation tests. For each network metric, we first calculated the between-group difference in terms of the mean network metrics. Then, we randomly reallocated all values into two groups and recomputed the mean differences between the two randomized groups. The permutation was repeated 10,000 times, and the 95th percentiles of the empirical distribution were used as the critical values for a two-tailed t -test of the null hypothesis with a probability of type I error of 0.05.

Regarding the multiple exploratory analyses of the nodal measures, the multiple comparisons correction was performed for nodal strength ($p < 0.05$, FDR-corrected).

The difference of RSFC between the familial and the sporadic groups were determined utilizing a network-based statistical (NBS <https://sites.google.com/site/bctnet/comparison/nbs>) approach. A primary threshold was applied to keep a subset of supra-threshold links. Then a corrected p -value was computed using the null distribution of the maximal connected component size, which was empirically derived from 10,000 nonparametric permutations. Further details of the NBS approach can be found in the prior work (Zalesky et al., 2010).

Reproducibility

The reproducibility of our results was addressed in terms of treatment of negative correlations, motion effect and comparison against health controls.

First, considering significant negative correlations found in many diseases, negative correlations were kept to analyze the functional connectomes including global measures and nodal measures.

Secondly, although no significant group difference was found between the familial and sporadic PD patients ($p > 0.05$) in terms of motion, the “scrubbing” method was used to substitute the frames with frame-wise displacement over 0.5 mm by linearly interpolating neighboring frames (Power et al., 2012). Then, the resulted “scrubbed” data were reanalyzed.

Thirdly, in order to investigate whether these abnormal functional connectomes are only present between the familial and sporadic PD patients, the difference of RSFC between PD patients and healthy controls were also studied (see Supplementary Material). A group of 38 age- and sex-matched healthy controls was analyzed, who showed no parkinsonian symptoms nor received any neuroleptic treatment.

RESULTS

Demographic and Psychometric Information

Demographic information, duration of disease, disease stage, UPDRS score and medications are summarized in **Table 1**. As shown in **Table 1**, there were no age or sex differences between two PD groups (two-sample t -test $p_{\text{age}} = 0.899$; Chi-square test $p_{\text{sex}} = 0.745$), and no between-group differences were found in the duration of disease (two-sample t -test, $p = 0.411$), MMSE (two-sample t -test, $p = 0.063$), H&Y score (two-sample t -tests, $p = 0.583$), or UPDRS score (two-sample t -test, $p = 0.490$). Compared with familial PD groups, sporadic PD patients scored higher in HAMD (two-sample t -tests, $p = 0.046$), which suggested sporadic patients showed more severe depression and anxiety.

Altered Network Organization of the Functional Connectome

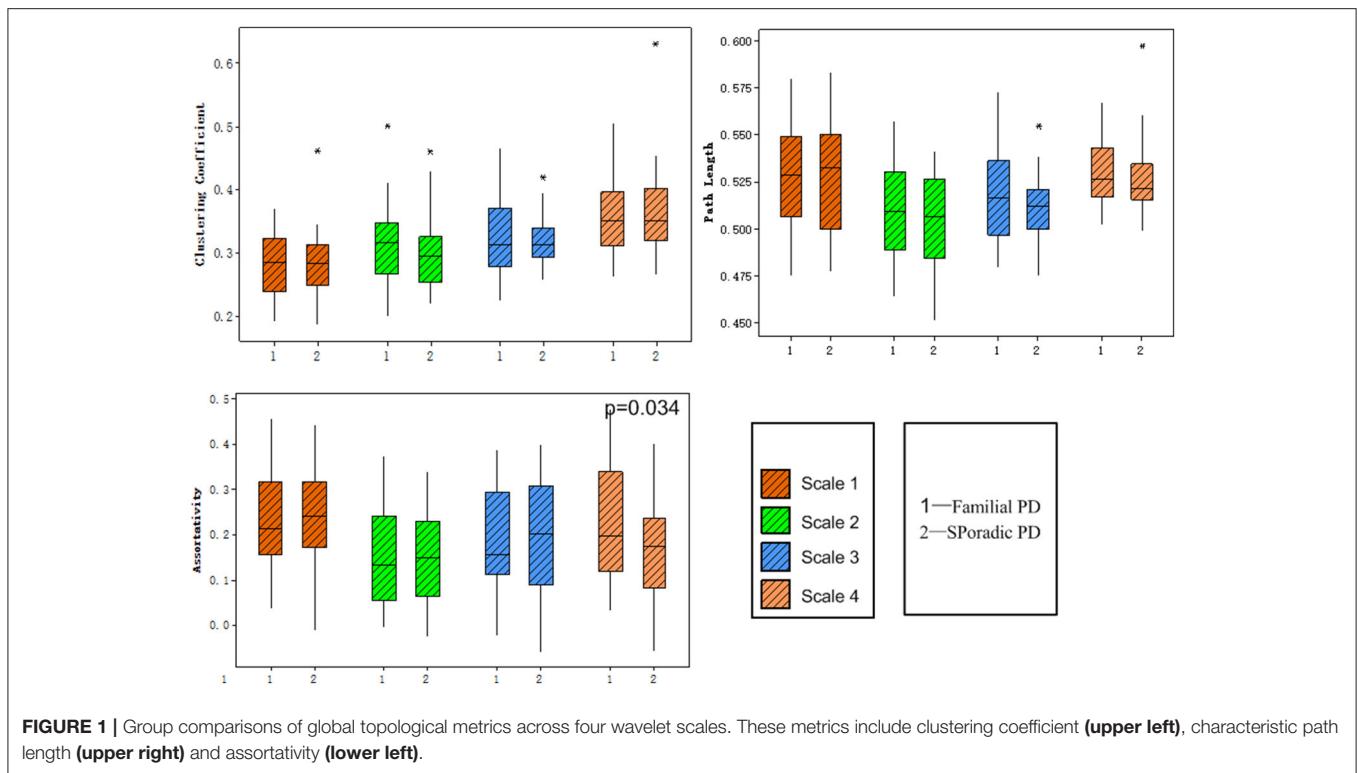
No significant group difference was found in terms of the total numbers of supra-threshold links or the mean wavelet coefficients in the wavelet correlation matrices on any scales. Both the familial PD group and the sporadic PD group exhibited typical property of small-world topology with $\gamma > 1$ and $\lambda \approx 1$. However, the familial PD group exhibited a significant increase in assortativity ($p = 0.034$) on the fourth wavelet scale (0.016–0.031 Hz) (**Figure 1**). A decreased nodal strength was observed in the left amygdala (medial amygdala) on the fourth scale (FDR-corrected $p < 0.05$, see **Figure 2**).

Using the NBS analysis, five decreased functional connections were revealed in the familial PD group on the fourth scale, under the primary threshold ($p < 1 \times 10^{-3}$). Moreover, as shown in **Figure 3**, the left amygdala (medial amygdala) was found as the center of those functional connections with decreased strength,

TABLE 1 | Clinical and demographic characteristics.

Index	FPD (n = 31)	SPD (n = 36)	p-value
Age (Y)	53.1 (± 9.97)	53.8 (± 11.7)	0.899*
Gender (m/f)	(17/15)	(21/15)	0.899*
Duration of disease (Y)	5.72 (± 4.00)	4.66 (± 4.53)	0.411*
Score of UPDRS	50.1 (± 26.4)	45.5 (± 23.1)	0.490*
Disease stage (H&Y)	2.39 (± 0.58)	2.27 (± 0.94)	0.583*
MMSE	28.13 (± 1.57)	25.57 (± 5.6)	0.063*
HAMD	6.65 (± 5.83)	11.18 (± 8.6)	0.046*
Side initially affected, L/R	17/14	19/17	0.5*
L-Dopa dose (mg/d)	434 \pm 242	333 \pm 243	0.174*
Percentage of patients treated with pramipexole	11	8	0.221*
Percentage of patients treated with piribedil	5	7	0.743*

Data are expressed as mean \pm SD. FPD-Familial Parkinson's Disease; SPD-Sporadic Parkinson's Disease; NC-Normal Control; H&Y, Hoehn and Yahr; UPDRS, Unified Parkinson's Disease Rating Scale; MMSE, Mini-Mental Status; HAMD, Hamilton Depression Scale. *Two-sample t -test; *Pearson χ^2 -test.



which connected to regions responsible for retrieval of motion information (Ueno et al., 2009) including the bilateral fusiform gyrus (medioventral area), left caudal lingual gyrus, right rostral lingual gyrus, and the right V5/MT+ area.

Reproducibility of the Results

As shown in **Table 2**, only on the fourth wavelet scale, significant group difference in network properties was found between the familial PD and sporadic PD group. Compared with sporadic PD, familial PD group showed significantly higher assortativity of weighted networks and the decreased nodal strength (FDR-corrected $p < 0.05$) in the left amygdala (medial amygdala).

On the fourth wavelet scale, compared with healthy control, sporadic PD patients also showed decreased assortativity. However, no significant difference in network properties was found between familial PD group and healthy controls (see Supplementary Material).

DISCUSSION

In this work, we explored the differences of topological organizations of the functional brain networks of subjects with sporadic and familial PD, and shed some light on the pathological mechanism impaired by this neurodegenerative disease. Compared to familial PD patients, altered functional connectome among sporadic PD group was found to predominant in the frequency band between 0.016 and 0.031 Hz, which is within the frequency range (0.01–0.073 Hz) of gray matter-related oscillations (Zuo et al., 2010). The alterations in functional organization between two PD groups can be characterized as

the following: (i) a decrease in assortativity, (ii) increased nodal degree in the left medial amygdala, and (iii) changed functional connectivity between the left medial amygdala and brain regions related to the retrieval of motion information.

It has been shown by a previous study that neuronal fluctuations are linearly distributed on the natural logarithmic scale (Penttonen and Buzsáki, 2003). Despite the exact underlying mechanism being poorly understood, aberrant topological architectures in some specific frequency bands reflected the change of brain complexity depending on the type of the information being processed (Hanslmayr et al., 2012; Fontolan et al., 2014). In terms of PD, it has been found that the abnormal amplitude of low-frequency fluctuations (ALFF) is present in the frequency interval of 0.01–0.027 Hz (Zhang et al., 2013). Recent studies have also highlighted the significance of this frequency band in other brain diseases. For example, increases of brain functional network efficiency caused by nicotine were found in the frequency band between 0.01 and 0.03 Hz, which suggested cholinergic effects on network topology (Wylie et al., 2012). Antisocial personality disorder patients exhibited altered topological configuration of the functional connectome in the frequency interval of 0.016–0.031 Hz (Tang et al., 2016). These previous findings along with our present results highlight the clinical significance of spontaneous neural fluctuations between 0.016 and 0.031 Hz.

In the further analyse, the assortativity metric within the abovementioned frequency range, which is a measure of brain network resilience (Newman, 2002, 2003), differentiated the sporadic PD group from familial PD group. Networks with positive assortativity are found to be more resilient with more

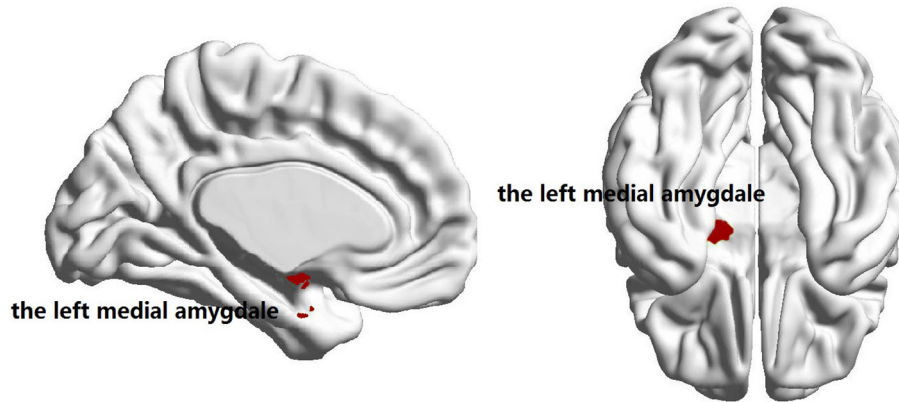


FIGURE 2 | Brain regions showing the decreased nodal degree in familial PD group compared with sporadic PD group ($p = 3 \times 10^{-5}$) on the fourth wavelet scale.

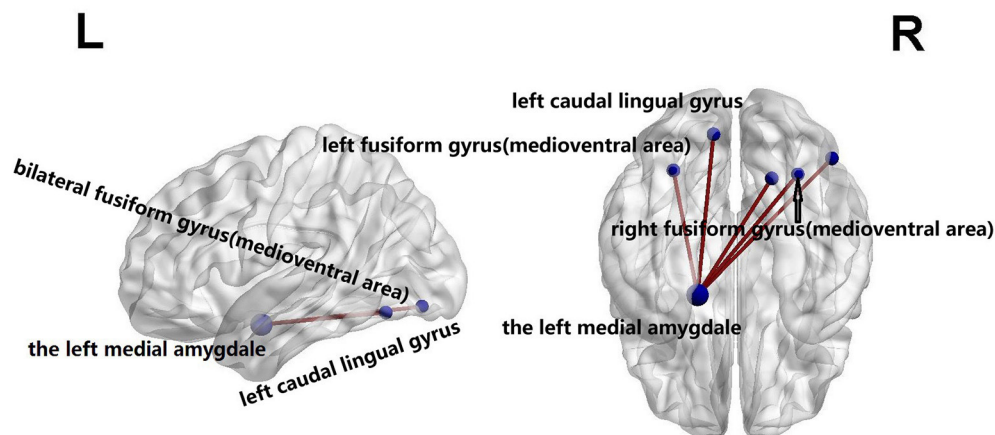


FIGURE 3 | Compared with sporadic PD, familial PD group showed a decreased functional networks strength according to the network-based statistical (NBS) analysis method, under a liberal primary threshold of ($p < 1 \times 10^{-3}$). The line represents the functional connection.

TABLE 2 | Comparisons of the global network metrics among the sporadic PD and familial PD on wavelet scale four.

		L_p	C_p	λ	γ	σ	Assortativities
familial PD	Case 0	0.530 ± 0.017	0.357 ± 0.061	1.004 ± 0.006	1.247 ± 0.184	1.241 ± 0.177	0.216 ± 0.114
	Case 1	0.716 ± 0.085	0.249 ± 0.096	0.716 ± 0.085	1.0261 ± 0.0610	1.458 ± 0.211	0.247 ± 0.132
	Case 2	0.529 ± 0.017	0.358 ± 0.060	1.004 ± 0.007	1.240 ± 0.181	1.234 ± 0.173	0.217 ± 0.116
sporadic PD	Case 0	0.527 ± 0.019	0.363 ± 0.068	1.004 ± 0.005	1.263 ± 0.201	1.258 ± 0.194	0.169 ± 0.114
	Case 1	0.771 ± 0.313	0.267 ± 0.115	0.771 ± 0.313	1.434 ± 0.276	1.434 ± 0.276	0.195 ± 0.126
	Case 2	0.526 ± 0.018	0.365 ± 0.068	1.004 ± 0.005	1.257 ± 0.205	1.252 ± 0.198	0.170 ± 0.109
p -value	Case 0	0.287	0.261	0.433	0.257	0.277	0.034*
	Case 1	0.261	0.254	0.433	0.267	0.361	0.039*
	Case 2	0.322	0.336	0.433	0.257	0.359	0.042*

Data are expressed as mean ± SD (* $p < 0.05$)

C_p : clustering coefficient; L_p : characteristic path length of a network; γ : normalized clustering coefficient; λ : normalized characteristic path length; σ : small-worldness index; Case 0, negative connectivities were set to zero and "scrubbing" method was not applied; Case 1, negative connectivities were kept; Case 2, the "scrubbing" method was applied to alleviate the effect of head motion.

mutually interconnected high-degree nodes. In healthy brain organization, higher assortativity signals higher resilience to random error (Achard et al., 2006). The decreased resilience observed in some pathological conditions is interpreted as a loss of network functionality (Liu et al., 2011; Haneef and Chiang, 2014). Furthermore, altered nodal strength was only observed in the left medial amygdala, which suggested changed blood flow and metabolism in that brain region (Liang et al., 2013). The amygdala, which is linked to both cortical and subcortical networks, exhibits significant pathological changes in PD, as Braak et al. (2006) demonstrated that the amygdala is involved in different stage of PD development. The amygdala, is involved in processing emotional stimuli and forming emotional memories (Phelps, 2006). The right amygdala is important for fear processing, and the left amygdala is responsible for processing sadness and anxiety (Kienast et al., 2008). Depressed PD patients showed increased left amygdala connectivity (Hu et al., 2015), which is coincident with our found that sporadic PD patients might experience more severe depression and anxiety (see HAMD score in **Table 1**).

It is also worth mentioning that the left amygdala (medial amygdala) was found to be the hub of altered connections. Those changed connections were between the left amygdala and regions related to the retrieval of motion information, e.g., the bilateral fusiform gyrus (medioventral area), left caudal lingual gyrus, right rostral lingual gyrus, and right V5/MT+ area (Ueno et al., 2009). The medial fusiform gyrus may play a vital role in the integration of multiple stimuli (Zhang et al., 2016), and the lingual gyrus is involved in the analysis of logical conditions (i.e., the logical order of events) (Fusar-Poli et al., 2009), whereas V5/MT+ area retrieves motion information (Rosen, 2003; Ueno et al., 2009; Tang et al., 2017). Those regions with significantly changed connectivities are in line with findings of previous studies. Namely, Herrera et al. (2012) showed PD patients with a deficit in the retrieval of motion-related semantic content, and Dujardin et al. (2001) found that memory and executive function were more impaired in patients with sporadic PD than familial PD patients. In our study, compared with the healthy controls, sporadic PD group had lower MMSE score. Besides genetic mutations as a major contributor to both forms of PD, sporadic PD patients are also vulnerable to risk factors such as age, drug abuse, and gene-environment interactions (Hirsch et al., 2013; Perez, 2015). The non-motor symptoms occur in both PD groups, but appear to be more benign in familial PD than in sporadic PD (Alcalay et al., 2011; Yokoyama et al., 2011; Ferrer et al., 2012). Thus all results consistently suggest the sporadic PD patients might be more impaired in terms of cognition and it potentially reflects the nondopaminergic

dysfunction in sporadic PD (Dujardin et al., 2001). Furthermore, the relative increases in functional connections in sporadic PD compared with familial PD group might provide evidence for the presence of compensatory neural mechanisms (Huang et al., 2007; Niethammer and Eidelberg, 2012) in sporadic PD patients relative to familial PD patients.

To our knowledge, our work is the first to explore frequency-dependent functional topological alterations between sporadic PD and familial PD. The difference of connectomes between sporadic PD and familial PD was identified and its pathological indication was discussed. Our findings not only provide novel insight into the neuropathological mechanisms of sporadic PD and familial PD but also highlight the potential clinical significance of frequency-dependent functional topology associated with different forms of PD.

AUTHOR CONTRIBUTIONS

YT, BT, and JG contributed to the conception and design of the study. LM, CW, ZL, and WL conducted clinical assessments and MRI data collection. YT, XX, and CW performed data analysis. YT, JG, and HX wrote and critically revised the manuscript. JG takes full responsibility for the work and decision making.

FUNDING

This work was supported by grants 81361120404, 81430023, and 81130021 from the National Natural Science Foundation of China (to BT), grants 81371405, 81571248 from the National Natural Science Foundation of China (JG), grant 2016CX025 from innovation-driven plan of Central South University (to JG). This work was also partially supported by grants 2016M592452, 2017T100613 from the China Postdoctoral Science Foundation and grants 2016JJ4090 from the Natural Science Foundation of Hunan Province (to YT). HX, XX, CW, LM, ZL, and WL report have no financial disclosures.

ACKNOWLEDGMENTS

The authors thank all patients and control subjects for their participation.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fnana.2017.00099/full#supplementary-material>

REFERENCES

- Achard, S., Salvador, R., Whitcher, B., Suckling, J., and Bullmore, E. (2006). A resilient, low-frequency, small-world human brain functional network with highly connected association cortical hubs. *J. Neurosci.* 26, 63–72. doi: 10.1523/JNEUROSCI.3874-05.2006
- Alcalay, R. N., Siderowf, A., Ottman, R., Caccappolo, E., Mejiasantana, H., Tang, M. X., et al. (2011). Olfaction in Parkin heterozygotes and compound heterozygotes: the CORE-PD study. *Neurology* 76, 319. doi: 10.1212/WNL.0b013e31820882aa
- Baria, A. T., Baliki, M. N., Parrish, T., and Apkarian, A. V. (2011). Anatomical and functional assemblies of brain BOLD oscillations. *J. Neurosci.* 31, 7910–7919. doi: 10.1523/JNEUROSCI.1296-11.2011
- Barzegaran, E., Joudaki, A., Jalili, M., Rossetti, A. O., Frackowiak, R. S., and Knyazeva, M. G. (2012). Properties of functional brain networks correlate

- frequency of psychogenic non-epileptic seizures. *Front. Hum. Neurosci.* 6:335. doi: 10.3389/fnhum.2012.00335
- Braak, H., Bohl, J. R., Müller, C. M., Rüb, U., de Vos, R. A., and Del Tredici, K. (2006). Stanley fahn lecture 2005: the staging procedure for the inclusion body pathology associated with sporadic Parkinson's disease reconsidered. *Mov. Disord.* 21, 2042–2051. doi: 10.1002/mds.21065
- Buzsáki, G., and Draguhn, A. (2004). Neuronal oscillations in cortical networks. *Science* 304, 1926–1929. doi: 10.1126/science.1099745
- Chai, C., and Lim, K.-L. (2013). Genetic insights into sporadic Parkinson's disease pathogenesis. *Curr. Genomics* 14, 486–501. doi: 10.2174/1389202914666131210195808
- Chao-Gan, Y., and Yu-Feng, Z. (2010). DPARSF: a MATLAB toolbox for “pipeline” data analysis of resting-state fMRI. *Front. Syst. Neurosci.* 4:13. doi: 10.3389/fnsys.2010.00013
- Ciceri, F., Rotllant, D., and Maes, T. (2017). Understanding epigenetic alterations in Alzheimer's and Parkinson's disease: towards targeted biomarkers and therapies. *Curr. Pharm. Des.* 23, 839–857. doi: 10.2174/1381612823666170124121140
- Desjardins, A. E., Kiehl, K. A., and Liddle, P. F. (2001). Removal of confounding effects of global signal in functional MRI analyses. *Neuroimage* 13, 751–758. doi: 10.1006/nimg.2000.0719
- Di Martino, A., Ross, K., Uddin, L. Q., Sklar, A. B., Castellanos, F. X., and Milham, M. P. (2009). Functional brain correlates of social and nonsocial processes in autism spectrum disorders: an activation likelihood estimation meta-analysis. *Biol. Psychiatry* 65, 63–74. doi: 10.1016/j.biopsych.2008.09.022
- Dujardin, K., Defebvre, L., Grunberg, C., Becquet, E., and Destée, A. (2001). Memory and executive function in sporadic and familial Parkinson's disease. *Brain* 124, 389–398. doi: 10.1093/brain/124.2.389
- Fahn, S., and Elton, R. L. (1987). “Unified Parkinson's disease rating scale” in *Recent Developments in Parkinson's Disease*, eds S. Fahn, C. D. Marsden, D. Calne, and M. Goldstein (Florham Park, NJ: Macmillan Health Care Information), 153–163.
- Fan, L., Li, H., Zhuo, J., Zhang, Y., Wang, J., Chen, L., et al. (2016). The human brainnetome atlas: a new brain atlas based on connectonal architecture. *Cereb. Cortex* 26, 3508–3526. doi: 10.1093/cercor/bhw157
- Fang, J., Chen, H., Cao, Z., Jiang, Y., Ma, L., Ma, H., et al. (2017). Impaired brain network architecture in newly diagnosed Parkinson's disease based on graph theoretical analysis. *Neurosci. Lett.* 657, 151–158. doi: 10.1016/j.neulet.2017.08.002
- Ferrer, I., Lópezgonzalez, I., Carmona, M., Dalfó, E., Pujol, A., and Martínez, A. (2012). Neurochemistry and the non-motor aspects of PD. *Neurobiol. Dis.* 46, 508. doi: 10.1016/j.nbd.2011.10.019
- Folstein, M. F., Folstein, S. E., and McHugh, P. R. (1975). “Mini-mental state”: a practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 12, 189–198. doi: 10.1016/0022-3956(75)90026-6
- Fontolan, L., Morillon, B., Liegeois-Chauvel, C., and Giraud, A.-L. (2014). The contribution of frequency-specific activity to hierarchical information processing in the human auditory cortex. *Nat. Commun.* 5:4694. doi: 10.1038/ncomms5694
- Fox, M. D., and Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat. Rev. Neurosci.* 8, 700–711. doi: 10.1038/nrn2201
- Fox, M. D., Zhang, D., Snyder, A. Z., and Raichle, M. E. (2009). The global signal and observed anticorrelated resting state brain networks. *J. Neurophysiol.* 101, 3270–3283. doi: 10.1152/jn.90777.2008
- Fusar-Poli, P., Placentino, A., Carletti, F., Landi, P., Allen, P., Surguladze, S., et al. (2009). Functional atlas of emotional faces processing: a voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. *J. Psychiatry Neurosci.* 34, 418–432.
- Goetz, C. G. (2003). The Unified Parkinson's Disease Rating Scale (UPDRS): status and recommendations. *Mov. Disord.* 18, 738–750. doi: 10.1002/mds.10473
- Göttlich, M., Münte, T. F., Heldmann, M., Kasten, M., Hagenah, J., and Krämer, U. M. (2013). Altered resting state brain networks in Parkinson's disease. *PLoS ONE* 8:e77336. doi: 10.1371/journal.pone.0077336
- Guo, J.-F., Xiao, B., Liao, B., Zhang, X.-W., Nie, L.-L., Zhang, Y. H., et al. (2008). Mutation analysis of Parkin, PINK1, DJ-1 and ATP13A2 genes in Chinese patients with autosomal recessive early-onset parkinsonism. *Mov. Disord.* 23, 2074–2079. doi: 10.1002/mds.22156
- Hacker, C., Perlmutter, J., Criswell, S., Ances, B., and Snyder, A. (2012). Resting state functional connectivity of the striatum in Parkinson's disease. *Brain* 35(Pt 12), 3699–3711. doi: 10.1093/brain/aws281
- Hamilton, M. (1960). A rating scale for depression. *J. Neurol. Neurosurg. Psychiatry* 23:56. doi: 10.1136/jnnp.23.1.56
- Haneef, Z., and Chiang, S. (2014). Clinical correlates of graph theory findings in temporal lobe epilepsy. *Seizure* 23:809. doi: 10.1016/j.seizure.2014.07.004
- Hanslmayr, S., Staudigl, T., and Fellner, M.-C. (2012). Oscillatory power decreases and long-term memory: the information via desynchronization hypothesis. *Front. Hum. Neurosci.* 6:74. doi: 10.3389/fnhum.2012.00074
- Hauser, D. N., and Hastings, T. G. (2013). Mitochondrial dysfunction and oxidative stress in Parkinson's disease and monogenic parkinsonism. *Neurobiol. Dis.* 51:35. doi: 10.1016/j.nbd.2012.10.011
- Herrera, E., Rodríguezferreiro, J., and Cuetos, F. (2012). The effect of motion content in action naming by Parkinson's disease patients. *Cortex* 48, 900–904. doi: 10.1016/j.cortex.2010.12.007
- Hirsch, E. C., Jenner, P., and Przedborski, S. (2013). Pathogenesis of Parkinson's disease. *Mov. Disord.* 28, 24–30. doi: 10.1002/mds.25032
- Hoehn, M. M., and Yahr, M. D. (1967). Parkinsonism: onset, progression and mortality. *Neurology* 17, 427–442. doi: 10.1212/WNL.17.5.427
- Hu, X., Song, X., Yuan, Y., Li, E., Liu, J., Liu, W., et al. (2015). Abnormal functional connectivity of the amygdala is associated with depression in Parkinson's disease. *Mov. Disord.* 30, 238–244. doi: 10.1002/mds.26087
- Huang, C., Mattis, P., Tang, C., Perrine, K., Carbon, M., and Eidelberg, D. (2007). Metabolic brain networks associated with cognitive function in Parkinson's disease. *Neuroimage* 34, 714. doi: 10.1016/j.neuroimage.2006.09.003
- Hughes, A. J., Daniel, S. E., Kilford, L., and Lees, A. J. (1992). Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J. Neurol. Neurosurg. Psychiatry* 55, 181–184. doi: 10.1136/jnnp.55.3.181
- Hughes, A. J., Daniel, S. E., and Lees, A. J. (2001). Improved accuracy of clinical diagnosis of Lewy body Parkinson's disease. *Neurology* 57, 1497–1499. doi: 10.1212/WNL.57.8.1497
- Kienast, T., Hariri, A. R., Schlagenhaut, F., Wrase, J., Sterzer, P., Buchholz, H. G., et al. (2008). Dopamine in amygdala gates limbic processing of aversive stimuli in humans. *Nat. Neurosci.* 11, 1381–1382. doi: 10.1038/nn.2222
- Kriegeskorte, N., Goebel, R., and Bandettini, P. (2006). Information-based functional brain mapping. *Proc. Natl. Acad. Sci. U.S.A.* 103, 3863–3868. doi: 10.1073/pnas.0600244103
- Li, Y., Yao, H., Lin, P., Zheng, L., Li, C., Zhou, B., et al. (2017). Frequency-dependent altered functional connections of default mode network in Alzheimer's disease. *Front. Aging Neurosci.* 9:259. doi: 10.3389/fnagi.2017.00259
- Liang, X., Zou, Q., He, Y., and Yang, Y. (2013). Coupling of functional connectivity and regional cerebral blood flow reveals a physiological basis for network hubs of the human brain. *Proc. Natl. Acad. Sci. U.S.A.* 110, 1929–1934. doi: 10.1073/pnas.1214900110
- Liu, J., Qin, W., Nan, J., Li, J., Yuan, K., Zhao, L., et al. (2011). Gender-related differences in the dysfunctional resting networks of migraine sufferers. *PLoS ONE* 6:e27049. doi: 10.1371/journal.pone.0027049
- Luo, C. Y., Guo, X. Y., Song, W., Chen, Q., Cao, B., Yang, J., et al. (2015). Functional connectome assessed using graph theory in drug-naïve Parkinson's disease. *J. Neurol.* 262, 1557–1567. doi: 10.1007/s00415-015-7750-3
- Lynall, M.-E., Bassett, D. S., Kerwin, R., McKenna, P. J., Kitzbichler, M., Muller, U., et al. (2010). Functional connectivity and brain networks in schizophrenia. *J. Neurosci.* 30, 9477–9487. doi: 10.1523/JNEUROSCI.0333-10.2010
- Maraganore, D. M., Harding, A. E., and Marsden, C. D. (1991). A clinical and genetic study of familial Parkinson's disease. *Mov. Disord.* 6, 205–211. doi: 10.1002/mds.870060303
- Maxim, V., Sendur, L., Fadili, J., Suckling, J., Gould, R., Howard, R., et al. (2005). Fractional Gaussian noise, functional MRI and Alzheimer's disease. *Neuroimage* 25, 141–158. doi: 10.1016/j.neuroimage.2004.10.044
- Murphy, K., Birn, R. M., Handwerker, D. A., Jones, T. B., and Bandettini, P. A. (2009). The impact of global signal regression on resting state correlations: are anti-correlated networks introduced? *Neuroimage* 44, 893–905. doi: 10.1016/j.neuroimage.2008.09.036
- Newman, M. E. (2002). Assortative mixing in networks. *Phys. Rev. Lett.* 89, 111–118. doi: 10.1103/PhysRevLett.89.208701

- Newman, M. E. (2003). Mixing patterns in networks. *Phys. Rev. E Stat. Nonlin. Soft Matter Phys.* 67(2 Pt 2), 241–251. doi: 10.1103/PhysRevE.67.026126
- Niethammer, M., and Eidelberg, D. (2012). Metabolic brain networks in translational neurology: concepts and applications. *Ann. Neurol.* 72:635. doi: 10.1002/ana.23631
- Palop, J. J., Chin, J., and Mucke, L. (2006). A network dysfunction perspective on neurodegenerative diseases. *Nature* 443:768. doi: 10.1038/nature05289
- Parkinson, J. (2002). *An Essay on the Shaking Palsy*. Sherwood, OR: Neeley & Jones.
- Penttonen, M., and Buzsáki, G. (2003). Natural logarithmic relationship between brain oscillators. *Thalamus Relat. Syst.* 2, 145–152. doi: 10.1017/S1472928803000074
- Percival, D. B., and Walden, A. T. (2006). *Wavelet Methods for Time Series Analysis*. Cambridge, UK: Cambridge University Press.
- Perez, X. A. (2015). Preclinical evidence for a role of the nicotinic cholinergic system in Parkinson's disease. *Neuropsychol. Rev.* 25, 371–383. doi: 10.1007/s11065-015-9303-z
- Phelps, E. A. (2006). Emotion and cognition: insights from studies of the human amygdala. *Annu. Rev. Psychol.* 57, 27–53. doi: 10.1146/annurev.psych.56.091103.070234
- Power, J. D., Barnes, K. A., Snyder, A. Z., Schlaggar, B. L., and Petersen, S. E. (2012). Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *Neuroimage* 59, 2142–2154. doi: 10.1016/j.neuroimage.2011.10.018
- Rosen, D. (2003). Amygdala abnormality and its role in autistic socio-emotional impairment: a proposed study of somatic intervention among macaque monkeys. *Concept* 27.
- Rubinov, M., and Sporns, O. (2010). Complex network measures of brain connectivity: uses and interpretations. *Neuroimage* 52, 1059–1069. doi: 10.1016/j.neuroimage.2009.10.003
- Sanz-Arigit, E. J., Schoonheim, M. M., Damoiseaux, J. S., Rombouts, S. A., Maris, E., Barkhof, F., et al. (2010). Loss of 'small-world' networks in Alzheimer's disease: graph analysis of FMRI resting-state functional connectivity. *PLoS ONE* 5:e13788. doi: 10.1371/journal.pone.0013788
- Skidmore, F., Korenkevych, D., Liu, Y., He, G., Bullmore, E., and Pardalos, P. M. (2011). Connectivity brain networks based on wavelet correlation analysis in Parkinson fMRI data. *Neurosci. Lett.* 499, 47–51. doi: 10.1016/j.neulet.2011.05.030
- Sporns, O., Tononi, G., and Kötter, R. (2005). The human connectome: a structural description of the human brain. *PLoS Comput. Biol.* 1:e42. doi: 10.1371/journal.pcbi.0010042
- Supekar, K., Menon, V., Rubin, D., Musen, M., and Greicius, M. D. (2008). Network analysis of intrinsic functional brain connectivity in Alzheimer's disease. *PLoS Comput. Biol.* 4:e1000100. doi: 10.1371/journal.pcbi.1000100
- Tang, Y., Long, J., Wang, W., Liao, J., Xie, H., Zhao, G., et al. (2016). Aberrant functional brain connectome in people with antisocial personality disorder. *Sci. Rep.* 6:26209. doi: 10.1038/srep26209
- Tang, Y., Meng, L., Wan, C.-M., Liu, Z.-H., Liao, W.-H., Yan, X.-X., et al. (2017). Identifying the presence of Parkinson's disease using low-frequency fluctuations in BOLD signals. *Neurosci. Lett.* 645, 1–6. doi: 10.1016/j.neulet.2017.02.056
- Tessitore, A., Amboni, M., Esposito, F., Russo, A., Picillo, M., Marcuccio, L., et al. (2012). Resting-state brain connectivity in patients with Parkinson's disease and freezing of gait. *Parkinsonism Relat. Disord.* 18, 781–787. doi: 10.1016/j.parkreldis.2012.03.018
- Thompson, P. M., Cannon, T. D., Narr, K. L., van Erp, T., Poutanen, V. P., Huttunen, M., et al. (2001). Genetic influences on brain structure. *Nat. Neurosci.* 4:1253. doi: 10.1038/nm758
- Ueno, A., Abe, N., Suzuki, M., Shigemune, Y., Hirayama, K., Mori, E., et al. (2009). Reactivation of medial temporal lobe and human V5/MT+ during the retrieval of motion information: a PET study. *Brain Res.* 1285, 127–134. doi: 10.1016/j.brainres.2009.06.025
- Wang, J., Zuo, X., Dai, Z., Xia, M., Zhao, Z., Zhao, X., et al. (2013). Disrupted functional brain connectome in individuals at risk for Alzheimer's disease. *Biol. Psychiatry* 73, 472–481. doi: 10.1016/j.biopsych.2012.03.026
- Wang, J. H., Zuo, X. N., Gohel, S., Milham, M. P., Biswal, B. B., and He, Y. (2011). Graph theoretical analysis of functional brain networks: test-retest evaluation on short- and long-term resting-state functional MRI data. *PLoS ONE* 6:e21976. doi: 10.1371/journal.pone.0021976
- Wylie, K. P., Rojas, D. C., Tanabe, J., Martin, L. F., and Tregellas, J. R. (2012). Nicotine increases brain functional network efficiency. *Neuroimage* 63, 73–80. doi: 10.1016/j.neuroimage.2012.06.079
- Yokoyama, H., Uchida, H., Kuroiwa, H., Kasahara, J., and Araki, T. (2011). Role of glial cells in neurotoxin-induced animal models of Parkinson's disease. *Neurol. Sci.* 32, 1–7. doi: 10.1007/s10072-010-0424-0
- Yu, R., Chien, Y. L., Wang, H. L. S., Liu, C. M., Liu, C. C., Hwang, T. J., et al. (2014). Frequency-specific alternations in the amplitude of low-frequency fluctuations in schizophrenia. *Hum. Brain Mapp.* 35, 627–637. doi: 10.1002/hbm.22203
- Zalesky, A., Fornito, A., and Bullmore, E. T. (2010). Network-based statistic: identifying differences in brain networks. *Neuroimage* 53, 1197–1207. doi: 10.1016/j.neuroimage.2010.06.041
- Zhang, W., Wang, J., Fan, L., Zhang, Y., Fox, P. T., Eickhoff, S. B., et al. (2016). Functional organization of the fusiform gyrus revealed with connectivity profiles. *Hum. Brain Mapp.* 37, 3003–3016. doi: 10.1002/hbm.23222
- Zhang, D., Wang, J., Liu, X., Chen, J., and Liu, B. (2015). Aberrant brain network efficiency in Parkinson's disease patients with tremor: a multi-modality study. *Front. Aging Neurosci.* 7:169. doi: 10.3389/fnagi.2015.00169
- Zhang, J., Wei, L., Hu, X., Zhang, Y., Zhou, D., Li, C., et al. (2013). Specific frequency band of amplitude low-frequency fluctuation predicts Parkinson's disease. *Behav. Brain Res.* 252, 18–23. doi: 10.1016/j.bbr.2013.05.039
- Zuo, X.-N., Di Martino, A., Kelly, C., Shehzad, Z. E., Gee, D. G., Klein, D. F., et al. (2010). The oscillating brain: complex and reliable. *Neuroimage* 49, 1432–1445. doi: 10.1016/j.neuroimage.2009.09.037
- Zuo, X. N., Ehmke, R., Mennes, M., Imperati, D., Castellanos, F. X., Sporns, O., et al. (2012). Network centrality in the human functional connectome. *Cereb. Cortex* 22, 1862–1875. doi: 10.1093/cercor/bhr269

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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