Altered dynamic functional network connectivity in levodopa-induced dyskinesia of Parkinson's disease

Qianqian Si

The First Affiliated Hospital of Nanjing Medical University

Yongsheng Yuan

The First Affiliated Hospital of Nanjing Medical University

Caiting Gan

First Affiliated Hospital of Nanjing Medical University

Min Wang

First Affiliated Hospital of Nanjing Medical University

Lina Wang

First Affiliated Hospital of Nanjing Medical University

Kewei Ma

First Affiliated Hospital of Nanjing Medical University

Kezhong Zhang (✉ kezhong_zhang1969@126.com)

First Affiliated Hospital of Nanjing Medical University <https://orcid.org/0000-0002-4437-1095>

Research

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Abstract

Background

Traditional measures of static functional connectivity may not completely reflect the dynamic neural activity of levodopa-induced dyskinesia (LID) in Parkinson's disease (PD). This study was aimed to investigate the dynamic changes of large-scale functional network connectivity in the temporal domain in PD patients with and without LID.

Methods

Using dynamic functional network connectivity (dFNC) analysis, we evaluated 41 PD patients with LID (LID group) and 34 PD patients without LID (No-LID group), on and off their levodopa medications. Group spatial independent component analysis, sliding-window approach and k-means clusters were employed.

Results

In OFF phase, we found no differences between PD subgroups in temporal properties. In ON phase, compared than No-LID group, LID group occurred more frequently and dwelled longer in strongly connected State 1, characterized by strong connections between visual network (VIS) and other networks. When switching from OFF to ON phase, LID group occurred more frequently and dwelled longer in State 2 and occurred less frequently and dwelled shorter in State 3 (both states were strongly connected), while No-LID group occurred more frequently and dwelled longer in State 5 (weakly connected). Additionally, correlation analysis further demonstrated that the severity of dyskinesia was only associated with frequency of occurrence and dwell time in State 2, dominated by inferior frontal cortex in cognitive executive network (CEN), strongly connecting with sensorimotor network (SMN) and VIS.

Conclusions

Using dFNC analysis, we found that compared to those without LID, PD patients with LID may be involved in the superexcitation of VIS, as well as interconnections between CEN and SMN, VIS, having impact on inhibition of motor circuits. The dFNC analysis might provide new insights into the neural mechanisms of LID in PD.

Background

In Parkinson's disease (PD), levodopa treatments could alleviate motor symptoms, but after 4–6 years, 40% of patients can induce one disabling motor complication of levodopa-induced dyskinesia (LID) [1, 2]. Idiopathic PD is considered as a disorder of response initiation characterized by excessive motor inhibition (i.e. akinesia, bradykinesia), while LID is primarily a clinical manifestation of disinhibition of

movements [3]. Previous neuroimaging studies on LID have discovered cortical morphological and functional alterations in inferior frontal cortex (IFC), one fundamental component of executive control or motor inhibition network [3–8]. However, the neural mechanisms behind this motor disorder remain poorly understood.

Traditional static functional connectivity (FC) on LID was measured with the assumption that intrinsic fluctuations during MRI scan were stationary.³ Nevertheless, recent studies have proposed that FC is dynamic or fluctuating within seconds to minutes, which highlights the need for detailed inspection of FC along discrete time windows [9–11]. Emerging data suggested the utility of dynamic functional network connectivity (dFNC) with sliding-window analysis for understanding functional neurodevelopment as well as PD pathogenesis [12–17]. Time-varying FC may reflect implied spontaneous changes in underlying networks, which might improve our knowledge of how neural systems flexibly coordinate to support cognitive and behavioral function. In addition, the interactions between large-scale brain networks in LID have not been examined in previous studies. Given that the human brain activity is complex and interconnected with the best balance between functional integration and specialization, the exploration for dynamic internetwork connectivity can provide insights into the abnormal functional integration and specialization of the brain in LID of PD.

Therefore, with dFNC analysis, this study was conducted to investigate the possible neural mechanisms behind LID. To be specific, we explored how large-scale functional network interactions changed dynamically in temporal domains (fractional windows, dwell time and number of transitions) of PD patients with and without LID when levodopa worked or didn't work. We hypothesized that compared to those without LID, PD patients with LID would display significantly different temporal properties in some specific brain states, and further these substantive differences would be associated meaningfully with the severity of dyskinesia.

Materials And Methods

Participants

In this study, 90 PD patients were consecutively recruited, of whom 50 were clinically diagnosed as LID (LID group), and 40 were patients without LID (No-LID group). All participants were corresponding to the United Kingdom Parkinson's Disease Society Brain Bank diagnostic criteria for idiopathic PD [18]. Inclusion criteria were: (1) a minimum six months duration of levodopa therapy; (2) presence or absence of LID after an acute levodopa test observed by the neurologist at the last examination; (3) stable levodopa medications dose for one month; (4) right handedness; (5) no use of anxiolytic, antidepressant, or antipsychotic drugs; (6) no evidence of cognitive impairment (mini-mental state exam (MMSE) score > 24); (7) no contraindications for MRI; (8) no evidence of brain tumor, vascular brain lesions, or brain atrophy; (9) no excessive head movements during the MRI scan; (10) the ability to tolerate 12 h withdrawal of dopaminergic medications before MRI session.

In LID group, all patients presented with peak-dose dyskinesia rather than diphasic dyskinesia or off-period dyskinesia. All participants gave their written informed consents. The research was approved by the ethics committee of the First Affiliated Hospital of Nanjing Medical University and completed in line with the Declaration of Helsinki.

Neuropsychological assessment

Clinical and neuropsychological assessments were performed in OFF and ON phase. Hoehn and Yahr (H-Y) staging scale and Unified Parkinson's Disease Rating Scale III (UPDRS III) were used to evaluate the severity of motor symptoms. The MMSE score was adopted to assess cognitive function. Total levodopa equivalent daily dose (LEDD) was calculated for each patient. Besides, Abnormal Involuntary Movement Scale (AIMS) was used to evaluate the severity of abnormal involuntary movements in LID group [19]. The complete demographic characteristics were listed in Table 1.

Table 1
Demographics and clinical characteristics of PD patients with and without LID

	LID	No-LID	P value
N	41	34	-
Age (years)	61.83 ± 9.29	60.53 ± 7.99	0.523 ^a
Gender (M/F)	22/19	21/13	0.494 ^c
Age at onset (years)	53.00 ± 9.55	55.50 ± 8.08	0.230 ^a
MMSE	27.93 ± 1.69	28.21 ± 1.39	0.542 ^b
Disease duration(years)	8.29 ± 4.12	5.74 ± 2.94	0.002^{b,*}
H-Y stage (OFF)	2.52 ± 0.51	2.34 ± 0.56	0.088 ^b
H-Y stage (ON)	2.17 ± 0.38	1.99 ± 0.51	0.077 ^b
LEDD, mg/day	730.8 ± 285.7	710.1 ± 383.4	0.309 ^b
UPDRS Σ (OFF)	37.07 ± 14.50	31.15 ± 15.86	0.096 ^a
UPDRS Σ (ON)	21.27 ± 9.27	17.41 ± 12.84	0.136 ^a
AIMS (ON)	9.12 ± 6.39	-	-
N: number; PD: Parkinson's disease; LID: levodopa-induced dyskinesia; No-LID: without levodopa-induced dyskinesia; M: Male; F: Female; MMSE: Mini-Mental State Examination; H-Y stage: Hoehn and Yahr staging; LEDD: Levodopa equivalent daily dose; UPDRS: Unified Parkinson's Disease Rating Scale; AIMS: Abnormal Involuntary Movement Scale.			
Data are given as mean ± standard deviation.			
^a Two-sample t-test.			
^b Mann-Whitney test.			
^c Chi-square test.			
* P < 0.05.			

MRI data acquisition

Images were obtained on a 3.0T Siemens MRI system (Siemens Medical Solutions, Germany). Structural 3D T1-weighted high-resolution images were obtained using the following sequence (repetition time (TR) = 1900 ms, echo time (TE) = 2.95 ms, flip angle (FA) = 9°, acquisition matrix = 256 × 256, field of view (FOV) = 230 × 230 mm², thickness = 1 mm, gap = 0 mm). Blood oxygenation level-dependent functional images were acquired with the following parameters: TR = 2000 ms, TE = 21 ms, FA = 90°, in-plane matrix

= 64×64 , FOV = 256×256 mm², thickness = 3 mm, gap = 0 mm, number of slices = 35, number of total volumes = 240.

The resting-state fMRI ran lasted about 8 minutes. During the MRI scan, participants were instructed to keep their eyes closed, stay awake, relax minds, and keep their heads still. All subjects were scanned twice in the same morning immediately before ('OFF phase': 12 h after last dopaminergic medication) and ~ 60 min after their usual morning levodopa dose ('ON phase'), in line with the expected time peaks of LID. The approximate time of LID onset was calculated according to patient's personal medication diary within the last week, which helped us to determine the individual time required for switching from OFF to ON phase. This information was then used to decide when to start fMRI acquisition on the day of the experiment. And scans were immediately ceased as long as maximal dopamine release triggered dyskinesia. To better capture this ON condition and avoid motion artefacts, patients were also consecutively monitored by clinicians inside the scanner room. Consistent with the studies using the same procedure [3, 4, 20], none of patients in LID group achieved dyskinesia during fMRI scan.

Resting state functional MRI preprocessing and head motion control

Data preprocessing was conducted using the SPM12 toolbox (<http://www.fil.ion.ucl.ac.uk/spm/>) implemented in MATLAB software (version R2016b, Math Works, Inc., Natick, MA, USA). The first ten scans were removed to allow for signal equilibration, resulting in 230 volumes. Then data were corrected for slice timing and head movements. The resulting images were normalized to the Montreal Neurological Institute template and resampled to $3 \times 3 \times 3$ mm³, and spatially smoothed with a Gaussian kernel of 6 mm full width at half maximum. To minimize potential head-motion bias, subjects were excluded if their mean framewise displacement values exceeded 0.5 mm, or maximum displacement in translation indexes x, y, or z was higher than 3 mm or in rotation indexes was higher than 3° [12, 21, 22].

Group independent component analysis

To create intrinsic networks, we performed spatial group independent component analysis (GICA) implemented in the GIFT toolbox (GIFT v4.0b; <http://icatb.sourceforge.net>). Subject-specific principal component analysis was applied to reduce data into 50 independent components (ICs), with the minimum description length criterion [15]. The stability and validity of ICs was ensured by repeating the ICA algorithm 20 times in ICASSO [23, 24]. Subject-specific spatial maps and time courses of each IC were created by the GICA back-reconstruction algorithm [25]. Of the 50 extracted ICs, relevant intrinsic connectivity networks were identified based on the criteria from Allen [9]. Firstly, we manually confirmed whether the peak activation clusters of spatial maps were located primarily in grey matter, no spatial overlap with vascular, ventricular, or susceptibility artefacts. Then we selected ICs with time courses dominated mainly by low frequency fluctuations (ratio of power below 0.1 Hz to 0.15–0.25 Hz), and with a high dynamic range in spectrum. This procedure resulted in 22 meaningful ICs, which were sorted into seven networks according to the spatial correlation values between ICs and the template [26]. As shown in Fig. 1A and Table S1, the seven networks contained basal ganglia (BG), auditory (AUD), sensorimotor

network (SMN), visual (VIS), cognitive executive network (CEN), default mode network (DMN), and cerebellum (CB).

The time courses of 22 ICs underwent additional postprocessing to remove remaining noise sources [15, 27]. Time courses were detrended, despiked using 3DDESPIKE algorithm, multiply regressed of the head movement parameters. Then temporal bandpass filtering with a high frequency cutoff of 0.1 Hz was performed. To obtain the static FC matrix, pair-wise Pearson's correlations were calculated and then transformed to z-values prior to further analysis (Fig. 1B).

Dynamic functional connectivity computation

The dFNC analysis was examined by applying two approaches: a sliding window approach and k-means clustering. A sliding window approach was adopted to estimate changes of FC over time, and the resulting windowed segments were used to calculate transient FC patterns. In our study, data were segmented into a sliding window of 30 TR [28–31], with a Gaussian window alpha value of 3 TR and a step size between windows of 1 TR. To promote sparsity, a penalty on the L1 norm was imposed utilizing the graphic LASSO framework by 100 repetitions [32]. To extract reoccurring FC patterns, we applied k-means clustering algorithm and iterated it 500 times. The similarity between window FC matrix and k-means cluster centroids was calculated using the L1 distance [9]. Based on the elbow criterion [9, 14], the optimal number of cluster states was determined to be five ($k = 5$), the so-called State 1, 2, 3, 4 and 5. According to the similarity with obtained five cluster centroids, all FC matrices of each subject were classified into one of the five states. .

To investigate the temporal properties of dFNC states, we computed three different variables [12, 13, 29]: (1) fractional windows, defined as the proportion of time for total subjects spent in each state; (2) mean dwell time, represents the time of participants staying in a certain state, which is calculated by averaging the number of consecutive windows spent in one state before switching to another state; (3) number of transitions, reflects overall number of transitions between states.

Statistical analyses

Statistical analyses were performed with IBM SPSS statistics 20.0 (Chicago, IL, USA). Normality of data was tested by Kolmogorov-Smirnov method. Two sample t-test was adopted for normally distributed variables. For non-normal distributions, Mann-Whitney U test was selected. All $p < 0.05$ were considered significant. Then, we performed Spearman's correlation analyses between temporal properties and the severity of dyskinesia (AIMS score) in LID group in ON phase, adjusting for several possible distractions [19, 33–35], including age at onset, LEDD and disease duration ($p < 0.05$, false discovery rate (FDR) correction).

Results

Demographic and clinical characteristics

We excluded a total of 15 patients, of whom 10 were due to excessive head movements and 5 were on account of incomplete scans. Eventually, the remaining 41 patients from LID group and 34 patients from No-LID group were included for further analysis. No significant differences were found in terms of age ($p = 0.523$) and gender ($p = 0.494$) between PD subgroups. However, disease duration was longer in LID group compared to No-LID group (8.29 ± 4.12 versus 5.74 ± 2.94 , $p = 0.002$). Hence, this factor was included as one of covariates in further correlation analysis. There were no other demographic and clinical differences between the two groups (Table 1).

Intrinsic connectivity networks

Spatial maps of all 22 ICs were shown in Fig. 1A. ICs were grouped into seven networks [12, 13]: BG (ICs 9, 10), AUD (IC 21), SMN (ICs 1, 4, 6, 24, 49), VIS (ICs 3, 11, 12, 37), CEN (ICs 34, 38, 41, 42, 50), DMN (ICs 14, 17, 46, 47), and CB (IC 2). Figure 1B displayed the static FC, which showed prominent positive within-network connectivity in SMN and VIS, as well as widely between-network interconnectivity. The detailed information of ICs was presented in Table S1.

Clustering analysis and dFNC patterns

Utilizing k-means clustering, we identified five dFNC states. As shown in Fig. 2A, the percentages of total occurrences of these states were a bit different, with State 5 more frequent (42%) than State 1 (12%), State 2 (13%), State 3 (11%) or State 4 (22%). To better visualize the patterns of outstanding dFNC differences between states, we kept connections with the most 5% strength [12, 15] of each state (Fig. 2B). State 1–5 shared the similarity in within-network connections of SMN and VIS, while they still possessed some unique between-network interconnection patterns. State 1 was prominently characterized by strong positive between-network connections in VIS-SMN, and negative between-network connections in VIS-DMN. Centred on CEN (particularly the IC 50), State 2 primarily exhibited strong positive between-network connections in CEN-SMN and negative between-network connections in CEN-VIS. For State 3, VIS took a vital role, which had strong positive connection with SMN and negative connections with DMN and BG. In State 4, interconnections were centred on CEN (particularly in IC 38 and IC 41), with strong between-network connections in CEN-DMN and positive between-network connections in CEN-SMN. Combining Fig. 2A and 2B, we found relatively weak within-network connectivity in SMN and VIS, as well as global neutral between-network connectivity in State 5.

Figure 3 demonstrated temporal properties (fractional windows, mean dwell time and number of transitions) for each state in OFF and ON phases. In OFF phase (Fig. 3A), there were no significant differences of temporal properties between LID and No-LID group. In ON phase (Fig. 3B), compared with No-LID group, LID group showed increased frequency of occurrence ($p = 0.042$) and dwell time ($p = 0.039$) in State 1 (characterized by strong connections between VIS and SMN, DMN). When switching from OFF to ON phase, LID group (Fig. 3C) occurred more frequently in State 2 (centred on CEN, strongly connecting with SMN and VIS) and occurred less frequently in State 3 (dominated by VIS, strongly connecting with SMN, DMN and BG). Meanwhile, LID group dwelled longer in State 2 and dwelled shorter in State 3. Nevertheless, when switching from OFF to ON phase, No-LID group (Fig. 3D) occurred more frequently

and dwelled longer in State 5 (lack of strong between-network connections). In terms of number of transitions, we did not find significant differences between groups. Overall, these findings suggested that, the stability of strong between-network connectivity (State 1, 2, 3) in LID group was significantly affected, while the expression of weak between-network connectivity (State 5) in No-LID group was increased.

Correlations between dFNC and the severity of dyskinesia in LID in ON phase

Previous studies have proposed that main risk factors for LID contained age at onset, LEDD and disease duration [19, 33–35]. After controlling for these covariates, we found that fractional windows and dwell time in State 2 of LID group were respectively positively correlated with AIMS score in ON phase (Fig. 4; $r = 0.481$, $p = 0.022$; $r = 0.426$, $p = 0.044$; FDR corrected). This indicated that the severer dyskinesia was, the more frequent occurrence and longer time were observed in State 2, dominated by network interactions between CEN and SMN, VIS. For other states, AIMS score was not significantly correlated with fractional windows and dwell time after FDR corrected. Besides, there were no significant correlations between AIMS score and number of transitions.

Discussion

In this study, dFNC analysis was used to explore the differences of dynamic functional network connectivity in PD patients with or without LID and on/off levodopa treatments, focusing on temporal properties (fractional windows, dwell time and number of transitions). Five states were identified across the entire sliding time windows. State 1–4 were less frequent but had strong within-network and between-network connections; State 5 was the most frequent characterized by relatively weak within-network connections and lack of strong between-network connections. Specifically, LID group occurred more frequently and dwelled longer in State 1 compared with No-LID group in ON phase. When switching from OFF to ON phase, frequency of occurrence of LID group increased in State 2 and decreased in State 3, correspondingly, dwell time of State 2 was longer and that of State 3 was shorter. While in No-LID group, only State 5 occurred more frequently and dwelled longer when levodopa medications worked. Further, correlation analysis indicated that the severity of dyskinesia in LID group was associated with frequency of occurrence and dwell time in State 2.

In this work, we did not focus on definite brain areas of interest as in previous LID studies [3], but examined FC of whole brain at the network level. Importantly, considering potential influence of dopaminergic medications on fMRI, we explored dFNC both in OFF and ON phases. Traditional static FC is used to analyze the average connectivity, implicitly assuming that FC remains constant throughout MRI scans. However, it is widely known that FC in human brain is dynamic. And spontaneous brain activity of LID patients, characterized by levodopa medications triggering involuntary movement, is considered as changing over scanning time. The dFNC can capture time fluctuations in network interactions and gain a deeper understanding of basic properties of brain networks [9, 12]. Emerging data suggested the important utility of dFNC for exploring underlying nerve damaged mechanisms such as migraine [14],

epilepsy [15], schizophrenia [16], and Alzheimer's disease [17]. In particular, for PD, Kim et al. proposed for the first time that PD patients occurred more frequently and dwelled longer in strongly between-network connected state compared to healthy controls [12]. Subsequently, they reported that increased dwell time in weak within-network connected state was associated with the presence of dementia in PD [13]. These findings implied that dFNC was a promising approach for clinical neuroimaging, and might provide greater insights into the neural mechanism of LID.

In this study, no significant differences of temporal properties were found between PD subgroups in OFF phase. In ON phase, compared to No-LID group, LID group occurred more frequently and dwelled longer in State 1. For State 1, interconnections were found between the VIS and other networks (strong positive connectivity between VIS and SMN, and negative connectivity of VIS with DMN). This indicated that LID may be related to the superexcitation of VIS. VIS is one of the most important sensory perception networks in humans. Since the aberrant processing of visual information has precise influences on motor impairments via sensory guidance [36, 37], the visual cortex is expected to be superexcitable in LID. However, the exact mechanism needs to be confirmed by further research.

The pathogenesis of LID is still not clear, but it is believed that aberrant dopaminergic modulation of basal ganglia-cortical motor loops in the direct and indirect pathways lead to overactivity of frontal cortical areas and the occurrence of peak-dose LID [5, 38, 39]. Our results showed that after controlling for associated covariates, the severity of dyskinesia was only closely linked with frequency of occurrence and dwell time in State 2, dominated by the IFC in CEN, strongly connecting with SMN and VIS. In general, the IFC has been included in a critical component of CEN, defined as the motor inhibition network, which has been shown to be connected with inhibitory control over motor responses, such as performance monitoring and implementing executive control [40, 41]. Long time levodopa treatment may pathologically alter the ability of IFC to monitor motor response and enhance the neural activity in motor cortex (the SMN in this study) either via cortico-basal ganglia pathway, or via cortico-cortical pathway [42]. Our results further confirmed the above hypothesis in terms of network level and dynamics of brain activity. CEN primarily comprising fronto-parietal regions is involved in key interactive functional networks for coordinating motor function [43]. It was reported that patients with LID was profoundly relevant to the dysfunction of cognition and execution (i.e. CEN) [44]. The SMN is involved in sensory perception and motor process [45, 46]. Studies identified that the disinhibition of cortical-subcortical circuits in the SMN may contribute to the abnormal involuntary movements [46]. It is conceivable that abnormal interconnections between CEN and SMN, VIS may have impact on inhibition of motor circuits, closely relating to the occurrence of LID [47, 48].

In agreement with previous studies [9, 12], our results revealed that State 5 was the highest frequency of occurrence, characterized by weak within-network connections and lack of strong between-network connections. The frequency of this more common state is thought to be related to the number of self-focused thoughts [49], while other states are considered to reflect cognitive, physiological or motion-related processes [50]. When switching from OFF to ON phase, the frequency of occurrence and dwell time of State 5 increased significantly in patients without LID, correspondingly resulting in the shortage of

time spent in other four strongly connected states. Thus, we speculated that when levodopa worked, PD patients without LID might prefer to remain in a calm state, which could be the reason for the absence of LID.

However, a few limitations have to be noted. First, head movements can have a bad effect on resting-state FC. To alleviate this influence, we performed a series of procedures, but the influence of head movements may not be completely ruled out. Second, similar to previous studies [35], the disease duration did not match well in our study, so we have considered this as one of covariates in further analysis to mitigate its effect. Third, to ensure the security of patients and avoid the impact of head movements on image quality, we begun fMRI scanning for those patients with LID before levodopa reached its peak in ON phase, which may not fully reflect the functional state of brain during the peak of dose.

Conclusion

To summarize, by the dFNC analysis, we found that the LID may be involved in the superexcitation of VIS, as well as abnormal interconnections between CEN and SMN, VIS, having impact on inhibition of motor circuits. We believe that the results from this study might facilitate our knowledge of understanding the neural mechanism of LID in PD.

Abbreviations

PD: Parkinson's disease; LID:levodopa-induced dyskinesia; IFC:inferior frontal cortex; FC:functional connectivity; dFNC:dynamic functional network connectivity; MMSE:mini-mental state exam; H-Y:Hoehn and Yahr; UPDRS:Unified Parkinson's Disease Rating Scale; LEDD:levodopa equivalent daily dose; AIMS:Abnormal Involuntary Movement Scale; TR:repetition time; TE:echo time; FA:flip angle; FOV; field of view; GICA:group independent component analysis; ICs:independent components; AUD:auditory; SMN:sensorimotor network; VIS:visual; CEN:cognitive executive network; DMN:default mode network; CB:cerebellum; FDR:false discovery rate.

Declarations

Availability of data and materials

The data are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

QS, YY and CG executed the research project and completed statistical analysis. QS wrote the first draft of the paper. MW acquired the data. KZ designed this study, revised the manuscript for intellectual content. All authors approved the final manuscript.

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Figures

Figure 1

The 22 independent components identified by group independent component analysis (A) Seven functional connectivity networks [basal ganglia (BG), auditory network (AUD), sensorimotor network (SMN), visual network (VIS), cognitive executive network (CEN), default mode network (DMN), and cerebellum (CB)] derived from the 22 independent components on the basis of their anatomical and functional properties. (B) Group averaged static functional connectivity between independent component pairs was calculated using the entire resting state data. The value in the correlation matrix represents the Fisher's z-transformed Pearson correlation coefficient. Each of the 22 independent components was rearranged by network group based on the seven functional networks.

Figure 2

Results of the clustering analysis in each state (A) Cluster centroids for five state. The total number of occurrences and percentage of total occurrences are listed above each cluster median. (B) Only 5% strongest connections (i.e. the largest absolute value correlation coefficients) in each state is displayed. Orange lines represent positive functional connectivity, and blue lines represent negative functional connectivity. BG = basal ganglia; AUD = auditory network; SMN = sensorimotor network; VIS = visual network; CEN = cognitive executive network; DMN = default mode network; CB = cerebellum network.

A Temporal properties of dFNC states for the LID and No-LID patients in OFF phase

B Temporal properties of dFNC states for the LID and No-LID patients in ON phase

C Temporal properties of dFNC states for the LID patients in ON and OFF phase

D Temporal properties of dFNC states for the No-LID patients in ON and OFF phase

Figure 3

Temporal properties for the PD patients with and without LID, in ON and OFF phases (A) Temporal properties of dFNC states for the LID and No-LID patients in OFF phase; (B) Temporal properties of dFNC states for the LID and No-LID patients in ON phase; (C) Temporal properties of dFNC states for the LID patients in ON and OFF phase; (D) Temporal properties of dFNC states for the No-LID patients in ON and OFF phase; Horizontal lines in dwell time indicate group medians. * $P < 0.05$, ** $P < 0.01$. PD: Parkinson's disease; LID: levodopa-induced dyskinesia; No-LID: without levodopa-induced dyskinesia; dFNC: dynamic functional network connectivity.

Figure 4

Correlations of AIMS score with temporal properties in the LID group during ON phase. The fractional windows and dwell time of State 2 was positively correlated with the AIMS score in LID group during ON phase ($P < 0.05$, FDR corrected). AIMS: Abnormal Involuntary Movement Scale.

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