Dynamic functional connectivity assesses the progression of Parkinson’s disease

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GRAPHICAL ABSTRACT

The dynamic functional connectivity (DFC) analyses suggested two states: a sparse FC state with high frequency and an intense FC state with low frequency.

The mean dwell time (MDT) of the sparse FC state decreased as PD progressed which positively correlated with neurological function deterioration.

The progression of Parkinson’s disease is accompanied by changes in brain dynamics.

PUBLIC SUMMARY

- Progression of Parkinson’s disease (PD) induces modulations in dynamic functional brain networks.
- Changes of dynamics functional brain network are linked to worsening PD symptoms.
- Dynamic brain network has potential as a biomarker for evaluating PD progression.
Dynamic functional connectivity assesses the progression of Parkinson’s disease

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INTRODUCTION

Parkinson’s disease (PD) ranks as the second-most prevalent neurodegenerative disorder. The primary etiology stems from dopamine neurotransmission deficits due to dopaminergic neuron degeneration in the substantia nigra, leading to a spectrum of motor and non-motor symptoms. As the disease evolves, these symptoms intensify, profoundly compromising patient well-being and safety. Gaining deeper insights into PD progression is pivotal for the timely introduction of therapeutic interventions, subsequently enhancing patients’ quality of life. However, there’s a pressing need for dependable biomarkers that can effectively track PD progression.

Resting-state (RS) functional connectivity (FC) MRI presents an invaluable tool to gauge the brain’s functional network status without the potential biases of task performance. Earlier studies have illuminated its potential in delineating disease progression trajectories. A study by Filippi M et al. showcased that longitudinal whole-brain FC variations differ among PD patients at various disease stages, observing a mix of hypo- and hyper-connectivity linked with symptomatic developments. This suggests that PD progression indeed instigates notable changes in the functional brain network, emphasizing a relationship between disease evolution and these functional shifts. Nevertheless, a majority of prior works overlooked the potential influence of PD progression on the patient’s dynamic functional connectivity (DFC) and its capability to monitor PD evolution.

Contrary to static FC, DFC encapsulates functional connectivity dynamics, often viewed as a more precise portrayal of neural networks. Preliminary cross-sectional analyses have highlighted significant deviations in the temporal facets of specific FC patterns in PD patients’ DFC compared to healthy counterparts, both globally and within the interplay between cortical and subcortical networks. Yet, the question remains: how does PD progression reshape the temporal dynamics and patterns of DFC? To unravel this, we utilized dual-timepoint clinical and RS-fMRI datasets at baseline and during a 1-4 year follow-up to probe DFC’s longitudinal shifts with PD evolution, utilizing a sliding windows strategy. This analysis encompassed the entire brain network and interactions between cortical subnetworks and the subcortical nucleus (SN), aiming to discern connections with clinical symptom amplification.

This study aimed to (1) Detect longitudinal shifts in DFC temporal properties across global brain networks during PD progression. (2) Unearth longitudinal transformations in DFC temporal properties within specific subnetwork partitions and SN amidst PD progression. (3) Associate these temporal properties changes with neurological function deterioration, aspiring to establish a groundbreaking biomarker for PD progression assessment.

MATERIALS AND METHODS

Data source

Participants’ data were sourced from the Parkinson Progression Markers Initiative (PPMI) database (http://www.ppmi-info.org). Local research ethics committees approved all PPMI-affiliated studies. Prior to the study’s commencement, every participant furnished written informed consent. This research incorporated only those patients who had available imaging (comprising fMRI and structural scans) and clinical assessment data. A total of 72 PD patients, who were subjected to dual-timepoint imaging and clinical evaluations at baseline and subsequent follow-up between 1 and 4 years, were included. Figure 1 delineates the process of data selection, processing, and analysis.

Clinical assessments

The PPMI dataset facilitated comprehensive motor and non-motor neurological evaluations of the patients. For a thorough longitudinal examination, we selected specific assessment scales, ensuring that they were implemented at both the evaluated timepoints. Daily non-motor and motor experiences were gauged using the Movement Disorder Society Unified Parkinson’s Disease Rating Scale part I (UPDRS-I) and part II (UPDRS-II). The UPDRS-III and IV scales determined PD’s motor signs and complications. Sleep disturbances were quantified via the Epworth Sleepiness Scale (ESS) and the Rapid Eye Movement Sleep Behavior Disorder Screening Questionnaire (RBDSQ), while the Montreal Cognitive Assessment (MoCA) evaluated cognitive impairments.

Image acquisition and preprocessing

To maintain result consistency and reliability, identical scanning parameters were used for imaging data at both timepoints. A 3.0-Tesla SIEMENS Prisma scanner was employed for image acquisition. Structural images were acquired using three-dimensional T1-weighted MPRAge with flip angle (FA) = 90°, matrix X = 256 pixels, matrix Y = 256 pixels, matrix Z = 176, pixel spacing X = 1 mm, pixel spacing Y = 1 mm, slice thickness = 1.2 mm, echo time (TE) = 2.9 ms, and repetition time (TR) = 2300 ms. RS-fMRI data were acquired using an echo-planar imaging sequence that lasted 7 min (210 volumes) with
Medicine

To normalize these maps, we were calculated between ROI pairs, producing FC maps with 216 x 216 pixels, pixel spacing X = 3 mm, pixel spacing Y = 3 mm, and slice thickness = 3 mm.

DPABISurf, a derivative of the DPABI/DPARSF toolbox designed for surface-based RS-fMRI data analysis, was employed for image data preprocessing. An exhaustive six-step process was utilized for MRI data processing, further elaborated upon in the supplemental information section.

Extract time courses for regions of interest

We used numerous cortical regions and SN as regions of interest (ROI). Cortical regions were mapped using the Schaefer 200 ROI cortical brain atlas. The 200 ROIs belong to seven brain networks, namely visual network (VN), sensorimotor network (SMN), dorsal attention network (DAN), ventral attention network (VAN), limbic network (LN), frontoparietal network (FTN), and default mode network (DMN). The SN were defined using the Tian 16 ROI subcortical brain atlas. The time series of the 216 ROIs were extracted. To avoid the effect of brain parcellations on the results, the cortical regions were also defined by the Schaefer 400 ROI cortical brain atlas and the Tian 16 ROI subcortical brain atlas.

Quality control for head motion

Prior to initiating the DFC analysis, a rigorous head motion quality check was undertaken. Any patient demonstrating a mean framewise displacement (FD) surpassing 0.2 mm was excluded from successive evaluations. A finalized cohort of 45 patients was established for subsequent analyses post exclusions.

DFC analysis of the whole brain network

Sliding window approach. The DFC analysis was conducted using a sliding window approach and the k-means clustering algorithm in the DynamicBC toolbox (version 2.2, http://www.restfmri.net/forum/DynamicBC). Based on prior research, we chose a 44-second window spanning 22 volumes, convolved with a 3 TR Gaussian kernel. This window moved in single TR increments across 200 volumes, resulting in 179 overlapping windows with a 96% overlap. Within this framework, Pearson linear correlation coefficients were calculated between ROI pairs, producing FC maps with 216 x 216 covariance matrices for each participant. To normalize these maps, we applied Fisher’s z transformation, yielding 179 dynamic FC maps per participant to represent DFC variations during scanning. For added robustness, we also employed the flexible least squares (FLS) method to generate a DFC map for every scan timepoint. Further details on the FLS approach can be found in the Supplementary Materials and Methods.

Clustering analysis. Based on prior research, we applied the k-means clustering algorithm to discern recurring FC maps, or “states”, gauged by their frequency and structure. By amalgamating all FC maps across subjects from both timepoints, a collective FC map of 16,110 windows was produced. To gauge the similarity between these FC maps, we employed the L1 Manhattan distance-effective high-dimensional data. To ascertain the optimal cluster count, three criteria were utilized: Calinski-Harabasz (CH), Davies-Bouldin (DB), and silhouette indices. The final optimal number of clusters was obtained by averaging the values obtained from the above three algorithms and rounding up. The optimal cluster number was determined by varying k from 2 to 10.

For the temporal dynamics of DFC, we examined mean dwell time (MDT), fractional window (FW), and number of transitions (NT). MDT gauges average continuity within the same state; FW signifies the ratio of windows in a specific state; and NT encapsulates state transitions for each participant. Variations in MDT, FW, and NT across PD patient timepoints were analyzed using paired t-tests (p < 0.05, FDR corrected).

DFC analysis of cortical subnetworks and SN

We investigated the DFC across the entire brain, encompassing all cortical areas and the SN. Furthermore, we separately analyzed each of the seven cortical subnetworks and the SN. For each subnetwork, we extracted the relevant time series and subsequently merged it with the SN’s time series, resulting in seven distinct time series. These were then subjected to DFC analysis using the sliding window approach and k-means clustering algorithm, maintaining consistent parameters as established earlier. We then contrasted the temporal properties of states across two observation points.

Relationship between neurological functions and temporal properties

To ascertain the link between the decline in neurological function and the longitudinal shifts in temporal properties, we executed a correlation analysis, juxtaposing the z-scored difference in neurological assessments with the z-scored difference in temporal properties. This analytical approach was employed in the DFC evaluation of the entire brain network, as well as in the examination of cortical subnetworks in conjunction with SN. A p-value of less than 0.05 was deemed statistically significant.

RESULTS

Demographic and clinical characteristics

In the final analysis, our cohort comprised 45 patients. We had to exclude 27 patients owing to excessive head movement, quantified as a FD greater than 0.2 mm. Both DFC data and clinical neurological evaluations were ascertained at two distinct timepoints for every participant, adhering to a within-subjects design paradigm. Table 1 delineates the comprehensive demographic and clinical profile of the participants.

DFC state analysis

Clustering analysis and the DFC states. Using optimal clustering criteria,
we discerned two distinct FC states, both consistently observed across individual scans and the patient cohort (Supplementary Figure 1). State I was characterized by sparse connectivity among brain regions, robust connections in specific between-networks (notably VN-DAN, SMN-DAN, SMN-VAN), and within networks like VN, SMN, and VAN. It manifested prominently, observed 9,881 times, and constituted 61.33% of all states (Figure 2A). In contrast, State II showcased broader, stronger inter-regional connections but was less recurrent, with 6,229 instances, representing 38.67% of all occurrences (Figure 2A). Notably, the prevalence of State I was statistically more significant than that of State II, with percentages of 63.33%±29.19% vs. 36.67%±29.19% (p<0.001).

Figure 3A and 3B show timepoint-specific FC states obtained using the k-means clustering analysis and the top 1% connections in each state, respectively. Similarly, the state I exhibited sparse FC between brain regions with strong connections in several between-networks (VN-DAN, SMN-DAN, and SMN-VAN) and within-networks (VN, SMN, and VAN). While state II showed stronger positive FC between brain regions.

Figures 3A and 3B display the timepoint-specific FC states determined through k-means clustering analysis and the dominant 1% of connections within each state, respectively. Analogously, State I demonstrated sparse FC amongst brain regions, coupled with pronounced connections in several between-networks such as VN-DAN, SMN-DAN, and SMN-VAN, and within the VN, SMN, and VAN networks. In contrast, State II was characterized by more intensified positive FC between brain regions.

Temporal properties of FC states in the two timepoints. We further delved into discerning whether the temporal attributes of FC states exhibited alterations concomitant with the progression of PD. Notably, the FW did not demonstrate significant temporal variations for either State I (0.63±0.30 vs. 0.60±0.30, p=0.42, FDR corrected, Figure 4A) or State II (0.37±0.30 vs. 0.40±0.30, p=0.42, FDR corrected, Figure 4B). However, a compelling difference was observed in the MDT for State I between the two timepoints. The MDT for State I at timepoint I was significantly truncated compared to timepoint II (58.38±11.06 vs. 39.93±4.02, p=0.004, FDR corrected, Figure 4B), implicating a reduction in dwell time for the sparse FC state as PD advanced.

Intriguingly, the state transitions’ frequency remained consistent across the timepoints (5.51±3.88 vs. 6.53±4.05, p=0.13, FDR corrected, Figure 4C). In a subsequent analysis aiming to establish associations between MDT decline and neurocognitive decline, a prominent positive correlation was identified: the diminishing MDT in State I was conjoined with exacerbated motor function decline (r=0.63, p<0.001, Figure 4D). This suggests that the deterioration in locomotor function is intertwined with a more pronounced decline in State I’s MDT.

DFC analysis of cortical subnetworks and SN. To explore the longitudinal alterations in DFC across individual cortical subnetworks and SN in PD patients, we employed a sliding window approach and clustering analysis on the time series data of each subnetwork and SN. Our results revealed a pattern parallel to whole-brain DFC. Specifically, DFC analyses within each subnetwork and SN isolated two salient FC states: a frequently occurring but sparsely connected state and a less common yet more robustly connected state (as evidenced in Figure 5A & 5D). Notably, deviations in temporal DFC properties were evident in VN-SN and VN-VN. In the VN-SN domain, the MDT for the sparse connections (termed State II) exhibited a marked reduction during timepoint II (40.77±47.66 vs. 24.52±16.93, p=0.023, FDR-corrected, Figure 5B). A parallel trend was discerned in VN-SN, with the MDT of sparse connections (State I) also diminishing significantly at timepoint II (36.21±37.96 vs. 23.36±17.61, p=0.023, FDR-corrected, Figure 5E). Further correlational analyses underscored that the MDT decline in LC-SN was associated with cognitive weakening (r=0.46, p=0.001, Figure 5C), and the MDT dip in VN-SN correlated with deteriorating motor function (r=0.72, p=0.001, Figure 5F) among PD patients.

To validate the robustness of our findings across varied ROIs and analytical techniques, we executed a DFC analysis using a sliding window approach for 416 ROIs and the FLS method for 216 ROIs. Consistent with our primary analysis, we observed analogous results (refer to Supplementary Figures 2-7). Specifically, the MDT of sparse FC states at timepoint II was significantly diminished compared to timepoint I. Further, a positive correlation emerged between the extent of MDT reduction in these sparse FC states and the decline in motor function. Comprehensive details of these observations are elaborated upon in the supplemental material. Collectively, these findings underscore the replicability and robustness of our results, suggesting they are not contingent on a specific methodological approach or parcellation scheme.

DISCUSSION

In this investigation, we delved into the longitudinal changes of DFC in PD patients by leveraging two-timepoint imaging alongside clinical neurological evaluations. Echoing findings from prior research,12,19 we discerned two distinct DFC states: a prevalent state characterized by sparse connections and a less frequent state marked by robust interconnections. Importantly, as PD advanced, the MDT associated with these sparse connections exhibited a pronounced decline. This reduction was positively aligned with the worsening of neurocognitive functions. To bolster the credibility of our outcomes, we employed diverse parameters and methodologies, underscoring the robustness...
PD is a multifaceted neurodegenerative disorder, rendering predictions regarding its progression challenging. While numerous studies have harnessed sophisticated neuroimaging techniques to pinpoint potential biomarkers for gauging PD progression, the practical applicability of these markers is still under scrutiny. This limited utility may stem from the constrained dimensions inherent in the neuroimaging data. DFC encompasses both spatial and temporal facets, underscoring the evolving nature of FC rather than a static portrayal, offering a more nuanced representation of functional brain networks. In our current endeavor, we employed DFC to monitor PD’s evolution, affirming its potential as a compelling biomarker for assessing PD progression. Specifically, a diminished MDT in sparse connections could be emblematic of PD’s advancement. These receding MDTs in sparse connections might hint at a scenario where PD progression adversely impacts the functionality of several between-networks (VN-DAN, SMN-DAN, SMN-VAN) and within-networks (VN, SMN, DAN).

Efficient cognition fundamentally relies on the integrative functions of between-network communication, while motor execution is underpinned by within-network communication. In our findings, a significant association was observed between the MDT decline in state I and motor exacerbation. This may be ascribed to diminished integrative function within the networks of VN, SMN, and DAN. Historically, PD has been linked to dysfunction in the visual network, engendering specific visual perturbations. Such disruptions can influence a spectrum of motor and non-motor behaviors, spanning from visuospatial function to the perception of gait functionality. Moreover, the cornerstone of PD diagnosis remains motor symptomatology, spurred by malfunctions in the sensorimotor area. Such dysfunctionality prompts FC alterations within the SMN, culminating in hindered sensorimotor integration. As PD advances, compounded by an escalated loss of these neurons, the FC anomalies within the SMN intensify. Furthermore, the DAN is posited to regulate the top-down voluntary attention allocation pivotal for task-specific motor execution. Holistically, an aberrant integrative function within the VN, SMN, and DAN networks correlates with the motor functional decline observed in PD patients – a resonance with prior research outcomes. Although our study detected reduced integrative function in certain between-networks (VN-DAN, SMN-DAN, SMN-VAN) within state I, a direct tie to cognitive function remained elusive, potentially attributable to the nuances of network parcellation. Still, it’s crucial to recognize the intimate interplay between DAN, VN, and SMN in modulating PD patients’ mobility. A
decline in VN-DAN FC might perturb the DAN’s regulatory role during visuospatial attention shifts, resulting in aberrant gait patterns in PD patients. Similarly, a reduced FC within SMN-DAN could hamper cognitive strategies pivotal for gait coordination. Collectively, these findings underscore the fluid nature of DFC, both within and across networks, as PD evolves, perpetuating a relentless decline in motor capabilities.

We investigated the longitudinal DFC variations in each of the seven cortical subnetworks and the salience network SN in PD. Altered temporal properties were particularly notable in the LN-SN and VN-SN. The LN, incorporating the orbitofrontal cortex and temporal pole, has regions like the hippocampus vital for cognitive functions. Established neural circuits link the SN with the limbic system, influencing cognitive processes like memory, learning, and emotion. Prior research highlights LN–SN pathway dysfunction in PD patients. Our findings emphasize the evolving DFC within this pathway, possibly mirroring the progressive cognitive dysfunctions in PD. Similarly, the VN-SN demonstrated a decline in the MDT of sparse FC states, strongly correlating with deteriorating motor function. Impairments within the VN-SN can indirectly cause motor dysfunction due to the pivotal role of the visual pathways in visuospatial construction and motion perception. Moreover, Guan et al. documented diminished functional connectivity between the occipital lobe and basal ganglia in certain PD phenotypes, emphasizing the connection between visual processing and motor symptoms. In essence, PD progression doesn’t only alter the DFC within the holistic brain network but also affects individual cortical subnetworks and the SN. This potentially elucidates the escalating spectrum of motor and non-motor symptoms in PD patients as the disease advances.

This study is not without limitations. Firstly, we did not include the longitudinal RS-fMRI data from healthy controls, limiting our ability to understand the impact of natural aging on longitudinal DFC changes. Secondly, it is well-established that dopaminergic medications affect RS-fMRI signals, as shown in DFC,26 studies. In the present study, due to limited data, we were unable to determine whether RS-fMRI acquisition and neurological functional assessments were performed during the medication-OFF. Thus, we can’t ascertain the magnitude to which our results may have been influenced by the effects of dopaminergic medications. But the effect of dopaminergic medication may be present in two timepoints, therefore, there would have been a balancing effect on the data across timepoints. Thirdly, our sample size was relatively small, suggesting that a broader sample might produce more definitive results. Lastly, our study did not delve into PD’s heterogeneity. Given that PD manifests differently among individuals, understanding these variations could provide deeper insights into its progression and impact.

In conclusion, our findings indicate that as PD advances, significant longitudinal shifts occur in the temporal aspects of DFC. Furthermore, these shifts
correlate directly with worsening neurological symptoms. This suggests that DFC holds promise as a valuable biomarker for assessing the progression of PD.

Values are presented as mean (SD). UPDRS = Unified Parkinson’s Disease Rating Scale. ESS = Epworth Sleepiness Scale. GDS-SF = Geriatric Depression Scale Short Form. RBDSQ = REM Sleep Behavior Disorder Screening Questionnaire. MoCA = Montreal Cognitive Assessment.

REFERENCES


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AUTHOR CONTRIBUTIONS

Fangang Meng, Yina Ma, Yang Li, Hua Zhang, revised the manuscript draft. In addition, we would like to thank our participants for generously taking part in this research. This work was supported by grants from the Natural Science Foundation of China (81971070) and the National Key Research and Development Program of China (2022YFC2405100).

DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AND MATERIALS AVAILABILITY

Data used in this Article are publicly available from the Parkinson’s Progression Markers Initiative database (www.ppmi-info.org/data).

SUPPLEMENTAL INFORMATION

It can be found online at https://doi.org/10.59717/j.xinn-med.2023.100027

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