REVIEW

Resting-State Functional Brain Networks in Parkinson's Disease

Hugo C. Baggio,[1] Bàrbara Segura[1] & Carme Junque[1,2,3]

1 Departament de Psiquiatria i Psicobiologia Clínica, Universitat de Barcelona, Barcelona, Catalonia, Spain
2 Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Catalonia, Spain
3 Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Hospital Clínic de Barcelona, Barcelona, Catalonia, Spain

SUMMARY

The network approach is increasingly being applied to the investigation of normal brain function and its impairment. In the present review, we introduce the main methodological approaches employed for the analysis of resting-state neuroimaging data in Parkinson's disease studies. We then summarize the results of recent studies that used a functional network perspective to evaluate the changes underlying different manifestations of Parkinson's disease, with an emphasis on its cognitive symptoms. Despite the variability reported by many studies, these methods show promise as tools for shedding light on the pathophysiological substrates of different aspects of Parkinson's disease, as well as for differential diagnosis, treatment monitoring and establishment of imaging biomarkers for more severe clinical outcomes.

Introduction

Parkinson's disease (PD) is a chronic progressive neurological process. Clinically, PD is mainly characterized by motor symptoms derived from the severe loss of dopaminergic neurons in the substantia nigra pars compacta. PD is not, however, merely a motor disease. Cognitive, neuropsychiatric and autonomic manifestations are highly prevalent and may precede the onset of motor symptoms [1].

For any given task, a host of distributed, functionally specialized brain areas work in concert to integrate sensorial inputs with previously stored information, as well as with executive and motor regions to generate an appropriate behavior. The set of brain regions that interact in this manner make up large-scale functional networks [2]. A network perspective of brain function, accounting for the interactions between regions, offers a potentially useful framework for the study of normal functioning and also for the identification of relevant intermediate pathological phenotypes [3]. Despite being in its early stages, the network approach applied to PD has shown potential clinical usefulness as a tool for differential diagnosis, monitoring disease progression, and treatment response, and also for the development of biomarkers for complications such as dementia. Noninvasive *in vivo* neuroimaging techniques also offer an unprecedented opportunity to characterize the pathophysiological substrates underlying different manifestations of the disease.

In the past decade, seminal studies [4–7] showed that coherent patterns of spontaneous neural oscillations are observed during "rest". The analysis of these oscillations reveals regions with correlated and anticorrelated activity, organized into large-scale intrinsic connectivity networks (ICNs). These networks display a highly robust pattern of connectivity, with high test–retest reliability [8–10], and a high correspondence with task-related networks [11]. Taken together, these data suggest that task-free or resting-state techniques are a useful tool to probe the brain's intrinsic connectivity architecture [12] with potential clinical applications. Of note, it has recently been demonstrated that the sites where invasive (i.e., deep-brain) stimulation and those where noninvasive (transcranial magnetic stimulation or transcranial direct current stimulation) are effective in PD can be shown to belong to the same brain networks through the analysis of resting-state data [13].

The number of studies addressing resting-state functional connectivity has increased considerably in the last few years, and the clinical impact of this type of analysis is currently being established. For these reasons, in this review we describe recent neuroimaging studies addressing alterations in PD through a network approach, mainly focusing on resting-state functional connectivity

studies. We put special emphasis on studies that searched for connectivity changes underlying cognitive deficits in PD, as there are currently no validated biomarkers for predicting or following these highly frequent and disabling complications. The studies included employed different methodologies, from the analysis of individual circuits or subsystems to whole-brain approaches, both through the assessment of ICNs and graph-theoretical techniques.

Cognitive Deficits in PD

Despite considerable interindividual variation, the vast majority of patients with PD develop cognitive impairments over time. By 20 years of disease duration, up to 80% of patients develop dementia [14], with a mean time from onset of PD to dementia of 10 years [15]. PD-related cognitive deficits are heterogeneous [16], mainly affecting attention and executive functions [17–20], memory [19,21], psychomotor speed [19,21], and visuospatial/visuoperceptual abilities [18,21,22]. Clinical presentations, response to therapy, and prognostic implications indicate the existence of two overlapping cognitive syndromes in PD: *frontostriatal deficits*, mainly related to dopaminergic imbalances [23]; and a *posterior cortical syndrome*, not related to dopamine deficiency. As the name implies, the latter syndrome is characterized by impairments with a putative posterior cortical basis, such as semantic fluency and visuospatial/visuoperceptual deficits [18]. Importantly, the posterior cortical syndrome, possibly related to gray matter synucleinopathy and/or Alzheimer's disease-type pathology [24], is associated with a higher risk of dementia [18,25,26]. Neuroimaging is probably the best tool to try to disentangle the neural underpinnings of both syndromes, with potential impact on risk stratification once disease-modifying treatments become available.

Resting-State Connectivity Analyses

Resting-state fMRI (RS-fMRI) connectivity methods are based on the temporal correlations of spontaneous blood oxygen level-dependent (BOLD) signal fluctuations between different brain areas [27–29]. Figures 1 and 2 describe two of the most frequently used approaches for connectivity analyses in RS-fMRI studies: seed-based analysis and independent component analysis (ICA). Given that dopamine plays a prominent role in striatal connectivity [30] and that dopaminergic deficits are responsible for many of PD's main clinical manifestations, the majority of RS-fMRI studies in PD have focused on the connectivity of striatal networks. More recently, other ICNs have also been evaluated [31,32].

Results from RS-fMRI studies in PD are not always consistent; this may be related to the inclusion of small study samples and variable use of methodological approaches, including image preprocessing steps such as global signal regression [33]. Additionally, head motion is often insufficiently reported and controlled for. Motion artifacts can bias connectivity estimates, and standard preprocessing methods may not be enough to correct them [34,35]. A discussion of state-of-the-art procedures to reduce these artifacts is beyond the scope of this review, but this issue is especially relevant when studying patients with movement disorders. Also, dopaminergic neurotransmission influences ICN functional connectivity [36,37] as well as network topology [38]. Consequently, medication status (i.e., *on*-state, *off*-state, or drug-naïve patients) certainly contributes to the variability in study findings. Finally, the manifestations of different clinical phenotypes of PD appear to have different functional substrates [39,40]. Clinical heterogeneity can therefore account for some of the variability in study findings.
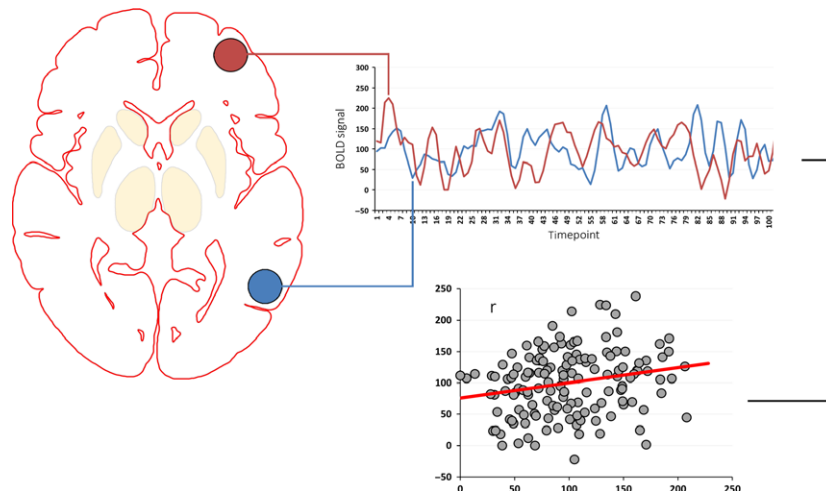
Figure 1 Seed-based correlation techniques are straightforward and easily interpretable methods in functional connectivity analysis [96] that necessitate *a priori* hypotheses for seed definition. Briefly, the mean time courses of regions of interest (ROI)—representing structures or circuits of interest, or the main nodes of ICNs—are extracted. In seed-to-seed (or node-to-node) techniques, the mean time course of each ROI is correlated with the mean time courses of every other ROI, limiting the analysis to the circuits of interest. Alternatively, in seed-to-whole-brain analyses, ROI time courses are used as regressors against the time courses of all voxels in the brain. Whole-brain *r*-correlation maps—in which the value assigned to each voxel is given by the correlation coefficient between its time series and the time series of the ROI in question—are thus generated, corresponding to the functional connectivity maps of each ROI. Subsequently, Fisher's *r*-to-*z* transformation is typically applied to ensure that the correlation coefficients are approximately normally distributed. The resulting connectivity maps are then analyzed using voxelwise statistical testing.
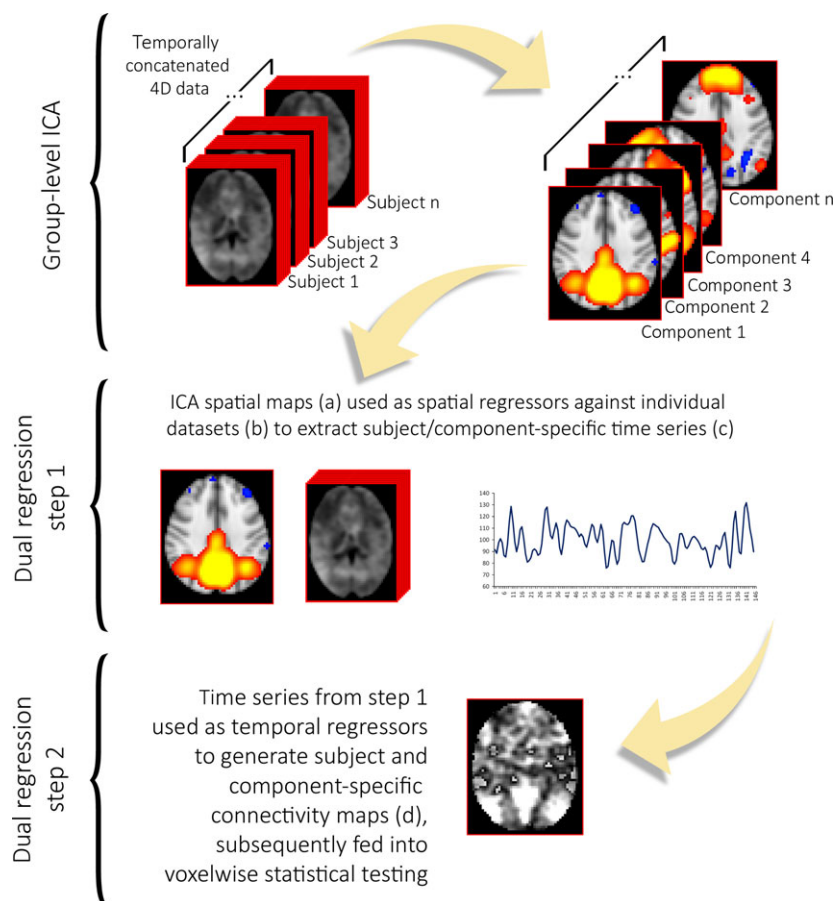
Figure 2 Independent component analysis (ICA) is a data-driven procedure that identifies coherent spatial signal fluctuation patterns in the dataset, extracting maximally independent components associated with the underlying signal sources—such as ICN and spatially structured artifacts—while avoiding the potential biases in the *a priori* selection of ROIs [105,107]. The number of components estimated in ICA (i.e., its dimensionality reduction) is a possible source of variability in study results as there is no single best approach for characterizing the complex hierarchy of ICN neurobiology [104]. Performing between-subject ICA analysis is not a straightforward procedure, as it is difficult to establish a direct, one-to-one correspondence of ICNs identified with individual-level ICAs [108]. Most current resting-state fMRI approaches involve performing group-level ICA on the temporally concatenated datasets of all subjects—allowing the extraction of subject-specific time courses and group-common spatial maps [108]. This is followed by the reconstruction of individual ICN maps through procedures such as dual regression or direct back-reconstruction techniques [104,108–110]. These methods minimize the problem of intersubject ICN correspondence and takes advantage of the higher signal-to-noise ratio offered by analyzing several subjects conjointly [104].

Striatal Functional Connectivity in PD

Studies using seed-to-whole-brain approaches have found reduced connectivity between the striatal nuclei, especially the putamen, and diffuse cortical/mesolimbic areas in patients with PD off medication [41–43]. In patients on medication, reduced connectivity with subcortical regions and increased connectivity with motor/premotor cortical areas have been described [43–45]. Baudrexel et al. [46] focused on subthalamic nucleus (STN) connectivity in *off*-state patients with PD. The authors found increased connectivity between the STN and primary sensorimotor cortical regions. A recent study confirmed these findings in early, drug naïve as well as in *off*-state moderate patients with PD [47].

A study by our group recently investigated frontostriatal connectivity changes associated with the presence of apathy in PD.

Patients were assessed on medication. We found apathy to be associated with connectivity reductions, mainly involving the left limbic frontostriatal circuit (i.e., ventral striatum and orbitofrontal cortex) [48].

Using ICA and dual regression, Szewczyk-Krolikowski et al. [49] described reduced connectivity between the basal ganglia network and widespread frontal, temporal, parietal cortical as well as striatal and brainstem regions in patients off medication compared with healthy controls as well as with patients on medication. These connectivity changes yielded an accuracy of 85% in differentiating patients from controls.

Finally, Kahan et al. [50] recently used a different approach to the study of resting-state connectivity in corticostriatal–thalamic pathways in PD. The authors assessed a sample of patients who had undergone STN deep-brain stimulation (STN-DBS), acquiring RS-fMRI data both with and without active

stimulation. Instead of functional connectivity, authors investigated the effects of STN-DBS on effective connectivity (which describes the causal influences of a region over another [51]), estimated through dynamic causal modeling [52]. They found STN-DBS to reduce the strength of effective afferents and efferents of the STN and to increase the sensitivity of the striatum to cortical afferents, the sensitivity of the cortex to thalamic afferents, and the connectivity of the direct pathway. Furthermore, strengthening of the direct pathway explained the most beneficial effects of STN-DBS.

Taken together, these study results indicate that dopamine deficits in PD lead to reduced overall functional corticostriatal connectivity and to increased connectivity in specific basal nuclei. Connectivity reductions mainly involve the portions of the striatum most affected by dopaminergic nigrostriatal denervation (i.e., the posterior putamen). Besides being related to the motor symptomology, functional connectivity changes are associated with nonmotor manifestations of PD such as apathy.

Default Mode Network Functional Connectivity in PD

The most studied cognitively relevant ICN in PD has been the *default mode network* (DMN). The DMN is mainly comprised of the precuneus/posterior cingulate cortex as well as medial prefrontal, inferior parietal and medial and lateral temporal cortical regions [53]. Initially described by Shulman et al. as a group of areas with reduced activity during active tasks and increased activity during passive conditions [54], the DMN is hypothesized to be related to self-referential processing [55]. The deactivation of DMN regions during encoding is related to subsequent retrieval of learned information [56]. Furthermore, DMN connectivity is relevant for externally directed attention and working-memory task performance [57]. Importantly, the overlap between DMN anatomy and the regions of hypometabolism in Alzheimer's disease (AD) led some authors to investigate pathological changes in this network. Subsequent studies showed patients with AD to have altered patterns of DMN activation/deactivation and abnormal functional connectivity between this network's main nodes [58–60]. Data from such studies in healthy and pathological populations led to the hypothesis that the DMN can be used as a predictive tool in neuroscientific research [61,62].

In PD, changes in the patterns of activation and deactivation of the DMN have been observed in task-based analyses [63,64]. Also, a positive effect of dopaminergic medication on intra-DMN connectivity has been suggested [65]. Gorges et al. [66] used a seed-to-seed approach to RS-fMRI DMN analysis and observed reduced functional connectivity between the medial PFC and the posterior cingulate cortex (PCC), as well as increased connectivity between left and right hippocampi. Comparing healthy controls and *on*-state PD patients with and without visual hallucinations through ICA followed by dual regression, Yao et al. [67] found reduced intra-DMN resting-state functional connectivity in both PD groups. Patients with hallucinations displayed connectivity increases in the right frontal pole and in the precuneus/PCC, compared with patients without hallucinations.

Other Large-Scale Intrinsic Connectivity Networks in PD

The analysis of resting-state data reveals the existence of other ICNs thought to be related to a broad range of neural functions, from sensory/motor to higher order cognition. Although the networks described are similar across studies, a uniform nomenclature has not yet been proposed. The *dorsal attention network* (DAN) is postulated to subserve externally directed cognition—more specifically, top-down allocation of attention [53,68]. The DAN is formed by the dorsolateral prefrontal cortex (PFC), frontal eye fields, inferior precentral sulcus, superior occipital gyrus, middle temporal motion complex, and superior parietal lobule [4,69]. The *frontoparietal network* (FPN) includes the lateral PFC, precuneus, inferior parietal lobule, medial superior PFC, and anterior insula. The FPN can flexibly connect to the DMN or the DAN depending on task nature and is hypothesized to mediate the dynamic balance between these networks [53,70]. Another network, the *salience* or *cingulo-opercular network*, mainly comprised of the anterior insula, the dorsal anterior cingulate cortex (ACC) and subcortical limbic structures, is believed to be related to reward/motivation processing [71].

Shine et al. assessed a sample of patients with PD on medication, divided according to the presence or absence of visual hallucinations, using a seed-to-seed approach and without a healthy control group. Patients with hallucinations displayed reduced resting-state connectivity between the ventral attention network and the DAN, and this reduction was associated with worse performance in the perceptual task. Patients with hallucinations also showed reduced functional connectivity between a DAN node (right dorsal ACC) and a DMN node (described as the left anterior interparietal lobule) [72]. Additional task-based fMRI analysis revealed that, when viewing monostable or bistable (ambiguous images that can be interpreted in two main ways) images, patients with hallucinations had reduced BOLD activation in areas belonging to the DAN. Furthermore, lower activation in the right frontal eye field (part of the DAN) was associated with increased misperceptions.

Recent studies have assessed the relationship between changes in ICN connectivity and cognitive measures. Using ICA, Tessitore et al. [32] found decreased intra-DMN resting-state connectivity in cognitively unimpaired patients with PD, assessed on medication, namely in the medial temporal lobe (associated with worse memory performance) and inferior parietal cortex (associated with visuospatial scores). In a study by our group [31], patients with PD on medication and a healthy control group were evaluated using seed-to-seed analyses as well as ICA and dual regression to assess changes in intra- and internetwork resting-state functional connectivity. Seed-to-seed analyses showed that worse cognitive status was associated with reduced connectivity within the DAN and the DMN and reduced DAN-FPN coupling. In ICA/dual regression analyses, PD patients with mild cognitive impairment (PD-MCI) were seen to have reduced connectivity between the DAN and right frontoinsular regions; these connectivity reductions correlated with impairments in attention/executive functions. The anterior insula is increasingly being recognized as a brain hub involved in processes of network switch that are relevant for attention

and executive functions [53,73,74]. Importantly, recent studies found that patients with PD-MCI have reduced insular dopaminergic D2 receptors and that this reduction correlates with impairments in executive functions [75]. In PD patients with visual hallucinations, reduced insular gray matter (GM) density associated with reduced functional connectivity between regions of the ventral attention network and the DAN has been described [72]. Combined with evidence that dopamine modulates resting-state patterns of coupling between cognitively relevant networks such as the DAN, the DMN, and the FPN [76], and these data seem to indicate that ICN changes (likely mediated by insular dopaminergic denervation) play a role in dopamine-related frontostriatal deficits in PD [77].

The association between changes in resting-state DMN connectivity and cognitive functions not related to dopamine imbalances (e.g., visuospatial) described by Tessitore et al. [32] suggests that the posterior cortical syndrome (related to global cognitive decline) also has detectable resting-state ICN correlates. Two recent studies seem to corroborate these findings [31,78]. In one study, we found that patients with PD-MCI had changes in occipito-parietal regions—namely cortical thinning, reduced connectivity with the DAN and loss of the pattern of anticorrelation with the DMN—which correlated with visuospatial deficits [31]. In another study, Olde Dubbelink et al. [78] used synchronization likelihood as a measure of coupling, assessing patients with PD on medication in a longitudinal design. The authors describe resting-state functional connectivity reductions, mainly involving posterior cortical regions, in association with global cognitive decline. They also describe a relationship between lower global mean connectivity levels and worsening cognitive status.

The observed association between posterior connectivity changes and structural degeneration [31] might indicate that disconnection is the result of primary cortical pathology. Nonetheless, axonal degeneration might antecede neuron cell body death in PD [79–81]. In this context, neuroimaging techniques such as diffusion-weighted imaging (DWI), which offers an *in vivo* indirect measure of microstructural white matter (WM) properties, have the potential to shed light on important aspects of PD-related pathological process.

Alterations in WM microstructure have been consistently described in PD through neuroimaging, often involving diffuse brain areas [82–89]. Agosta et al. [89] found widespread WM fractional anisotropy (FA—a marker of WM microstructural organization that tends to be reduced in pathological processes) reductions in PD-MCI subjects compared with healthy controls. Similarly, Melzer et al. [84] found that patients with MCI and dementia had diffuse FA decrements and mean diffusivity (MD —a microstructural parameter that tends to increase in WM disease) increments. Current evidence regarding the relationship between topographical WM changes and specific cognitive manifestations in PD is limited. Using a small patient sample and no control group, Zheng et al. [86] found that executive functions and language correlated with FA and, inversely, with MD in frontal WM tracts; attention was associated with DTI measures in widespread regions. Future studies, combining structural and functional connectivity techniques, could help clarify the role played by structural disconnection in the functional network alterations observed in PD.

Whole-Brain Topology

Current neuroimaging techniques allow a complete, whole-brain mapping of structural and functional interregional connections, *that is*, the connectome (Figure 3A) [90]. The comprehensive study of large, complex datasets such as the human neuroimaging connectome necessitates systematic analytical approaches that provide quantifiable and biologically meaningful measures. In the context of complex network analysis, graph theory is a robust mathematical framework that can characterize the functional or structural properties of the brain by modeling it as a single network [91]. Within this framework, functional neural networks—the graphs—are a collection of anatomical brain regions (nodes). In a functional graph, the connection (described in a graph as an edge) between a pair of nodes is defined by the temporal dependency of these nodes' signal variations.

Nodes are the basic elements of a network assumed to represent its functional units. As neuroimaging methods can only probe the macroscalar organization of the connectome, network nodes should be defined by regions as functionally homogeneous as possible, with a coherent connectivity pattern [91]. There is currently no consensual approach to define brain nodes through neuroimaging. As different parcellation strategies can yield different topological properties [92], networks obtained through different schemes are not quantitatively comparable [91]. To further complicate the interpretability of graph theory studies, the neuroimaging modality employed and other methodological aspects—such as the use of binary or weighted graphs and the thresholding approach used—can influence the topology of the reconstructed networks [93–96]. Graph theory metrics inform on different global and local network properties; basic network measures are described in Figure 3B.

To this date, very few studies have evaluated patterns of resting-state connectivity in PD using graph theory approaches, and most used RS-fMRI. Lebedev et al. assessed drug-naïve patients with PD through RS-fMRI as well as with Ioflupane (^{123}I) (DaT-SCAN) imaging in a subsample. Worse performance in executive function tests was associated with lower nodal strength (sum of individual strengths of a node's links) in dorsal frontal and parietal regions. Additionally, this pattern correlated with nigrostriatal dopaminergic function. Memory performance, on the other hand, correlated with strength in prefronto-limbic regions and was not associated with dopaminergic innervation [97]. Assessing patients on medication, Göttlich et al. used different parcellation schemes and applied a density threshold range of 10–35% to construct binary networks. The authors found significantly higher normalized clustering coefficients and characteristic path lengths in the PD group at 10 and 15% density. No correlations, however, were performed between network parameters and clinical variables [98]. In a study by our group, assessing *on*-state patients and using a weighted network approach, no topological differences were found between healthy controls and the total PD sample. Stratifying the patient group according to cognitive status, patients with PD-MCI were seen to have increased non-normalized clustering as well as modularity and small-world coefficients. In the overall PD sample, these measures correlated negatively with cognitive performance, namely in memory and visuospatial/perceptual functions. Additionally, network hubs displayed reduced
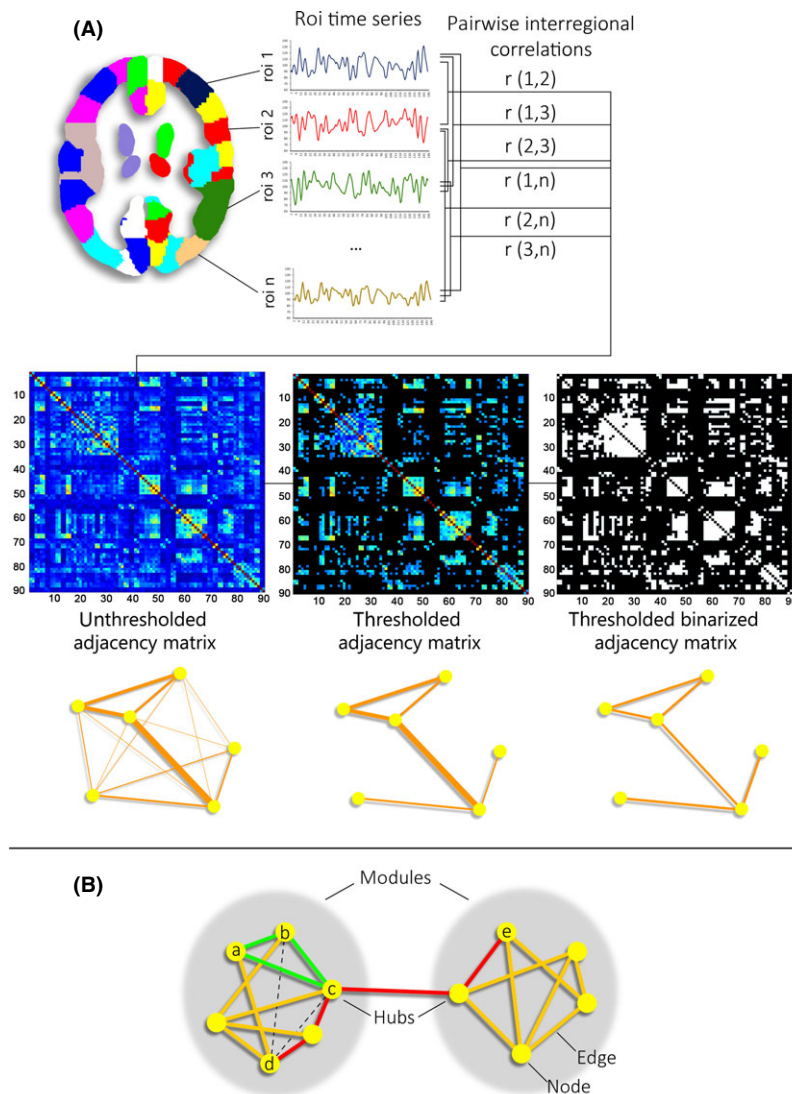
Figure 3 Panel **A**: Definition of functional brain networks. In its simplest form, the functional connectivity between a given pair of nodes is defined by the Pearson correlation between their respective time series. An adjacency matrix representing all internodal correlation coefficients is subsequently thresholded to discard weak, possibly noise-related connections. There is no universally accepted approach for thresholding, however. The use of fixed strength thresholds can result in graphs with different connection density, making intersubject comparisons difficult [94]. Fixed density thresholds, on the other hand, can be inappropriate in the presence of significant overall connectivity differences [94]. The resulting graphs will be weighted if correlation strength is taken into account. Otherwise, binary graphs are generated. Panel **B**: Global and nodal network metrics. In the small network shown, the red line indicates the shortest path between nodes *d* and *e*. The characteristic path length of a node informs about how closely connected this node is to all other network nodes. It is given by the average shortest path length between itself and every other node, or, in its binary form, the average number of edges that need to be traversed in order to get from this to any other node [95]. Network integration is given by the global characteristic path length (average of the characteristic path lengths of all nodes). The clustering coefficient of node *a* is represented by the number of triangles formed with its neighboring nodes (*b*, *c*, and *d*) [111]. Only one triangle (green, *a-b-c*) is present out of three possible triangles (dashed lines, *a-b-d* and *a-c-d*), yielding a clustering coefficient of 1/3. The clustering coefficient describes how interconnected a node's neighbors are. The global clustering coefficient, given by the average of the clustering coefficients of all nodes in a network, is a measure of local connectedness or network segregation. A balance between global characteristic path length and clustering coefficients defines small-world networks, characterized by high local specialization and some global shortcuts, allowing fast information transfer [111,112]. The human connectome displays small-world topology in both functional and structural networks [112,113]. The degree of a node (number of input or output connections linked to it) describes this node's accessibility within the network [114]. Degree in neural networks follows a heavy-tailed distribution, indicating the existence of a set of highly connected or hub nodes [115]. Hubs are hypothesized to be relevant for overall information transfer [116] and appear to be preferentially affected in several disorders [117]. Finally, the measure of modularity indicates how well a network can be subdivided into well-defined modules or communities made up of densely interconnected nodes with few intermodular connections, possibly representing the network's functional subcomponents. The small network shown contains two modules, connected by two connector hub nodes.

centrality in patients with PD-MCI, suggesting a reorganization of functional network traffic away from these brain regions [99]. Assessing connectivity through wavelet correlation and using a weighted network approach, Skidmore et al. [100] found reduced local and global efficiency in a small sample of patients with PD off medication compared with controls. No correlations were performed with measures of disease severity.

In contrast with the RS-fMRI studies described above, Olde Dubbelink et al. [101] used MEG to assess topological changes over time in a longitudinal design. Patients with PD were evaluated on medication, and baseline assessments included a drug-naïve subsample. Longitudinal analyses revealed progressive reductions in normalized clustering coefficients at multiple frequency bands and reductions in normalized characteristic path lengths at the alpha2 band in the patient group. The apparent discrepancy observed between these clustering coefficient reductions and the increases described in RS-fMRI studies may be related to the differential sensitivity to local connectivity displayed by different imaging modalities [102,103].

Conclusions

The studies discussed in the present review show that resting-state connectivity techniques, under a network perspective, are capable of identifying changes related to different clinical aspects of PD. In broad terms, these findings indicate that PD is accompanied by dopamine-dependent functional connectivity disruptions in corticostriatal–thalamic–cortical networks that underlie both motor and nonmotor symptoms. The pattern of connectivity of other ICNs is also altered in PD. Within- and between-network disruptions involving the DMN, the DAN, the FPN, and the ventral attention network seem to be associated with cognitive deficits and visual hallucinations. Dopaminergic and structural changes in the insula, a region involved in network switch, appear to be involved in these network abnormalities. General cognitive decline is also accompanied by long-range functional connectivity reductions, possibly with a differential involvement of posterior cortical regions. Future studies combining structural and functional techniques should investigate whether alterations in structural connectivity contribute to these functional changes.

In graph-theoretical analyses, the entire network organization is condensed into abstract topological parameters. The biological interpretation of the corresponding metrics, however, is often not straightforward. The combined use of methods that assess topographical changes, such as those discussed in the previous paragraph, can provide a more complete depiction of the reconfiguration of functional networks underlying clinical deficits in PD. The study of the connectome as a complex network is a recent field, and the relationship between different measures of network communication and brain function is only beginning to be unveiled. Advances in connectomics, including the use of multimodal approaches, the development of standardized procedures to reconstruct biologically consistent networks, as well as of mathematical models to interpret brain networks in physiologically meaningful ways, will determine the extent to which graph theory approaches become reliable tools from a clinical standpoint.

It is also clear that there is considerable variability in study results. Appropriate interpretation demands that sample characteristics be taken into account, especially with regard to treatment status and disease severity. Discrepant results are certainly due in part to the use of different methodological approaches, sensitive to different features of the pathological process and to different aspects of the complex interactions between functional networks. Susceptibility to confounds also varies according to the methodology used. Univariate approaches such as seed-based correlation are insensitive to the statistical relationship between data points and are more susceptible to structured noise or to be confounded by spatial network overlap than multivariate methods such as ICA [104,105]. Seed-based correlation is still useful, however, to answer specific research questions. Likewise, the potential effects of confounding factors such as motion artifacts on computed graph theory network metrics cannot be overstated. In light of recent publications, it is critical that new studies apply rigorous measures to control the effects of head motion and other nonneural sources of signal variation, from subject exclusion to "cleanup" fMRI preprocessing procedures [35,106].

In conclusion, neuroimaging network approaches are a promising tool in the study of PD, with the potential to shed light on relevant aspects of the neurodegenerative process and to provide useful biomarkers for more severe disease progression.

Acknowledgments

Conflict of Interest

The authors declare no conflict of interests.

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