Review

Functional Connectivity Signatures of Parkinson's Disease

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Abstract. Resting-state functional magnetic resonance imaging (RS-fMRI) studies have been extensively applied to analyze the pathophysiology of neurodegenerative disorders such as Parkinson's disease (PD). In the present narrative review, we attempt to summarize the most recent RS-fMRI findings highlighting the role of brain networks re-organization and adaptation in the course of PD. We also discuss limitations and potential definition of early functional connectivity signatures to track and predict future PD progression. Understanding the neural correlates and potential predisposing factors of clinical progression and complication will be crucial to guide novel clinical trials and to foster preventive strategies.

Keywords: Functional MRI, imaging, biomarkers, Parkinson's disease, resting-state networks

INTRODUCTION

Parkinson's disease (PD) is a chronic neurodegenerative disorder with a point prevalence ranging from 0.25–4% between age of 65–80 [1]. Degeneration of nigrostriatal dopaminergic neurons resulting in disruption of basal ganglia–thalamo-cortical loops, underlies the classical motor signs and symptoms of PD. The typical motor PD signs may be preceded by a period that lasts several years to decades, in which the neurodegeneration process is already started and spreads throughout the nervous system [2]. This early phase is characterized by a broad range of slight motor and/or non-motor features (i.e., hyposmia, sleep disturbances, mood disorders, pain, etc.), or might even have no clinical expression. In this phase a clinical diagnosis of PD as for current diagnostic criteria [3] is not allowed. However, this prodromal stage is gaining more attention as neuroprotective treatment in early stages could prevent clinical PD from emerging, revolutionizing the history of disease [2].

After a clinical diagnosis has been made, dopamine replacement therapy (DRT) is the most effective treatment for patients with PD [4]. However, DRT is complicated by the evolution of motor complications, including motor response fluctuations and levodopa-induced dyskinesias (LID) [5], which may develop progressively, with up to 80% of levodopa-treated patients showing involuntary movements after 4–6 years of treatment, and up to 90% after 10 years [6, 7]. Risk factors for developing LID include long treatment duration, high initial dose of levodopa, young age at onset, low body weight, female sex, but yet these factors alone cannot predict whether an individual patient will develop LID [6].

As the disease progresses, cognitive function in PD deteriorates over time [8], severely influencing the motor outcome as well as the patients' quality of

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life and prognosis [8, 9]. The spectrum of cognitive symptoms in PD is heterogeneous, ranging from mild cognitive impairment (MCI) to dementia (PDD) [9]. In one long-term study, dementia was present in 83% of those patients surviving for > 20 years [10].

Currently, premotor diagnosis as well as prediction of PD complications is one of the main goal of the current PD research. In this framework, neuroimaging techniques such as functional MRI (fMRI) have recently provided several insights into the pathophysiology of PD and some suggestions about treatment and progression-related changes.

Functional connectivity is defined as the temporal coherence of neuronal activity patterns emerging from anatomically separated brain regions [11], and therefore is thought to rely and express the functional communication between them. The blood oxygen level dependent (BOLD) signal provides a link between the neuronal activity, arising during information processing, and the MRI signal strength. As it has been demonstrated that the BOLD signal reflects the firing of neural populations with a strong correlation between its amplitude and local field potentials data [12], it has been suggested that BOLD signal is more related to synaptic activity rather than neural activity per se, providing information about the processing of neuronal information at the synaptic level.

During the last decade, researchers have assessed the spontaneous oscillations of the BOLD signal at rest in both healthy and pathological brain [13, 14], revealing the presence of consistent 'intrinsic' resting-state (RS) spatially distributed functional connectivity networks, called RS networks (RSNs). Compared to task-based fMRI, RS-fMRI allows to study simultaneously different networks, improving the chances to detect disease-related connectivity disturbances.

The spontaneous fluctuations of RS BOLD signals are generally low frequency oscillations, observed between 0.01 and 0.08 Hz frequency band [13]. Recent studies have shown that these low frequency temporal components reflect spontaneous fluctuations of brain physiology and metabolism [15, 16].

Several analytic approaches have been applied to study the RSNs [17, 18]. Seed-based approach is a common method to investigate the functional connectivity between a preselected seed or region of interest (ROI) and other brain voxels. Thus, seed-based studies provide information about the functional coupling between the averaged BOLD time course of a predetermined seed and the BOLD time courses of other voxels across the whole brain. This method requires

an *a priori* hypothesis, and a rigorous selection of appropriate ROIs. Independent component analysis (ICA) is the most common data-driven method to isolate functional connectivity networks from fMRI data and does not necessarily need a previous assumption. This method can be applied to assess the spatial distribution of the coherence of BOLD signals across all brain voxels [19], within the most reported and investigated RSNs (Fig. 1):

– Default-mode network (DMN): it is involved in introspection, mind-wandering, active episodic memory and becomes deactivated during specific goal-directed behavior. It encompasses mainly precuneus and posterior cingulate, bilateral inferior–lateral–parietal and ventromedial frontal cortices.
– Sensorimotor network (SMN): it has a central role in detection and processing of sensory input and preparation and execution of motor functions. It comprises the primary sensorimotor cortex, supplementary motor area (SMA) and secondary somatosensory cortices.
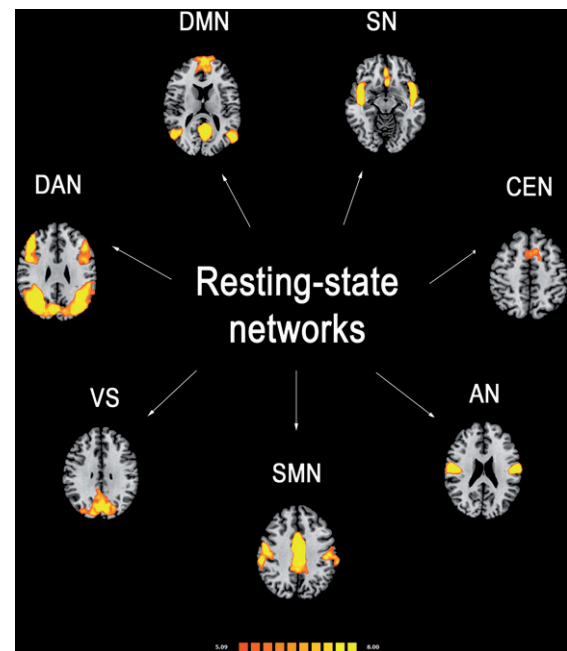

Fig. 1. Most reported resting-state functional connectivity networks in healthy controls. Mean resting-state functional MRI imaging networks shown in axial view and three-dimensional reconstructions ($p < 0.05$ corrected). Colors represent percentage BOLD signal change, overlaid on the average anatomic images in standard space. DMN, default-mode network; SN, salience network; CEN, central executive network; DAN, dorsal attention network; SMN, sensorimotor network; VS, visual network; AN, auditory network.

– Central executive networks (CEN): it is involved in executive control and working memory function and operates across mesiofrontal areas, including anterior cingulate and para-cingulate cortices.
– Salience network (SN): it detects and responds to behaviorally salient events and encompasses manly the dorsal anterior cingulate cortex and bilateral insulae.
– Dorsal attention (DAN): it is involved in voluntary (top-down) orienting and selective attention. Superior parietal and superior frontal areas, including intraparietal sulcus and frontal eye-fields are the most involved cortical areas;
– Auditory network: it is involved the right and left primary auditory cortex, Heschl's gyrus, lateral superior temporal gyrus and posterior insular cortex.
– Visual network: cortical areas involved in this network and function are mainly the lateral and superior occipital gyrus as well as the lingual gyrus.

Several studies have shown the presence of a functional reorganization within these networks in PD patients [20], but how each network interacts to the others has been also investigated. Indeed, specific functional coupling/decoupling patterns have been shown between the RSNs [21, 22], and this seems to be crucial for the so-called neurocognitive networks (i.e., DMN, CEN, SN, DAN), which are critical to generate and maintain an efficient behavioral and cognitive performance [22, 23].

Another analytic method for RS-fMRI data is the graph theoretical analysis. With this approach, anatomic brain regions are considered to be nodes, linked by edges, which represent the connectivity measured by the temporal correlation of BOLD fluctuations between the nodes. To date, only a few RS-fMRI studies using graph theoretical approach have been conducted in patients with PD [24–31] with a degree of inconsistency between studies mostly related to the small number of subjects or the inclusion of subjects across different PD stages.

It is important to note that at this stage caution needs to be taken in the context of translation RS-fMRI into clinical practice. Indeed, to date there is a lack of standardization of RS-fMRI acquisition and analysis methods and concerns about its reliability have been raised [32, 33]. In PD patients, reproducibility of functional connectivity alterations has been the focus of a recent study by Badea and colleagues [32] where three independent RS-fMRI datasets have been analysed with the same workflow. Only a few brain regions showed marginally consistent functional connectivity changes across all three datasets, with a very low impact from technical issues [32]. However, as the three PD samples were clinically heterogeneous in terms of disease duration and medication status, this may highlight the sensitivity of RS-fMRI in detecting specific neural changes which characterize each disease stage and the effect of dopaminergic treatment on both connectivity and BOLD signal variability.

Some studies also suggest the presence of specific RS-fMRI features at individual level which may also differ from what revealed by group comparisons, with a high rate of reliability across independent datasets [34]. However, RS-fMRI is still not able to provide a comprehensive disease picture at the individual patient level nor to offer ratable measures to compare one single subject to another or to a group of controls.

Nevertheless, other reports have shown high within-subject longitudinal reproducibility of RSNs, suggesting that they might potentially serve as biomarkers for monitoring disease progression [35].

In summary, RS-fMRI is a widely available, non-invasive and cost-effective tool which needs technical and methodological improvements to confirm its potential to support the clinical diagnosis and track PD progression biomarkers.

In this review, we attempt to summarize the most relevant studies supporting the role of RS-fMRI imaging as a potential biomarker of PD pathology and disease progression. We also discuss the prospects for incorporating these biomarkers into future clinical trials to track treatment response and predict complications.

SEARCH STRATEGY

Articles published on PubMed until December 2018 were checked for the purpose of this review. "Parkinson's disease" were cross-referenced with "resting state functional magnetic resonance imaging". Two independent observers (RDM and AT) evaluated the results, excluding duplicates and articles judged irrelevant by title and abstract screening. The same raters performed the quality check of selected studies and the most relevant ones for the topic were finally included in this narrative review (Table 1).

Table 1
Summary of the methods and results from the studies included in the review

Reference	Imaging methods	Subjects	Main findings
Diagnosis of PD and motor symptoms correlates			
Sang et al., 2015 [24]	Graph-analysis	26 early PD patients vs 30 HC	Decreased global efficiency in PD compared to HC. Increased nodal centrality in bilateral pallidum, inferior parietal lobule, and medial superior frontal gyrus, and decreased nodal centrality in caudate nucleus, supplementary motor areas, precentral gyrus, and middle frontal gyrus in PD compared to HC
Berman et al., 2016 [25]	Graph-analysis	19 PD patients vs 16 HC	Increased local efficiency in CEN and SN. Levodopa significantly decreased local efficiency in PD in all networks except within the putamen and caudate
Fang et al., 2017 [27]	Graph-analysis	26 early PD vs 19 HC	Decreased nodal degree, global efficiency, local efficiency and characteristic path length within the SMN and VN in PD compared to HC. Higher nodal degree, global efficiency and local efficiency, and lower characteristic path length within DMN and cerebellum in PD compared to HC. Lower cluster coefficient in thalamus and caudate nucleus in PD compared to HC
Suo et al., 2017 [28]	Graph-analysis	153 PD vs 81 HC	Decreased clustering coefficient, global efficiency, and local efficiency, and increased characteristic path length as well as decreased nodal centralities in the SMN, DMN, and temporal-occipital regions in PD compared to HC
de Schipper et al., 2018 [30]	Graph-analysis	107 PD vs 58 HC	Increased eigenvector centrality within frontoparietal regions in PD compared to HC. Increased connectivity in the SMN and VN in PD compared to HC.
Hou et al., 2018 31]	Graph-analysis	20 early akynetic PD vs 20 HC	Lower nodal centralities in the occipital lobe and areas of the limbic system and higher nodal centralities in frontal and temporal regions in PD compared to HC
Tuovinen et al., 2018 [51]	Graph-analysis	16 early PD vs 16 HC	At baseline, increased connectivity between cerebellum and SMN as well as decreased connectivity between motor regions and cingulate cortex in PD compared to HC. At 1.5 years follow-up, increased cerebellum connectivity within itself and to the caudate nucleus, thalamus and amygdala in PD compared to HC
Wu et al., 2009 [42]	Seed-based analysis (M1, bilateral cerebellum, SMA, cingulate motor area, globus pallidus, putamen, thalamus, parietal cortex, and DLPFC)	22 PD vs 22 HC	Decreased functional connectivity in the SMA, left DLPFC and left putamen as well as increased functional connectivity in the left cerebellum, left M1, and left parietal cortex in PD compared to HC. Levodopa relatively normalized functional connectivity in PD
Wu et al., 2011 [43]	Seed-based analysis (pre-SMA and M1)	18 PD vs 18 HC	Increased connectivity between pre-SMA and M1 as well as decreased connectivity between pre-SMA and putamen, right insula, right premotor cortex, and left inferior parietal lobule in PD patients compared to HC

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Baudrexel et al., 2011 [46]	Seed-based analysis (STN)	31 early PD vs 44 HC	Increased connectivity between STN and cortical motor areas in PD compared to HC
Hacker et al., 2012 [50]	Seed-based analysis (anterior and posterior putamen, caudate)	13 advanced PD vs 19 HC	Decreased striatal connectivity with thalamus, midbrain, pons and cerebellum in PD compared to HC. Decreased functional connectivity in sensori-motor and visual areas as well the supramarginal gyrus in PD compared to HC
Agosta et al., 2014 [45]	Seed-based analysis (caudate and putamen nuclei, globus pallidus, and thalamus)	69 PD (25 early PD) vs 27 HC	Decreased connectivity within striatal and thalamic regions as well as increased connectivity between striatum and temporal cortex, and between thalamus and several sensorimotor, parietal, temporal, and occipital regions in PD patients compared to early PD and HC
Manza et al., 2016 [49]	Seed-based analysis (putamen, caudate and their subregions)	62 PD (23 drug-naïve)	Higher motor impairment at baseline and over 1 year was correlated with decreased coupling between anterior putamen and midbrain. Higher decline in cognitive function was associated with increased coupling between the dorsal caudate and the rostral anterior cingulate cortex
Jech et al., 2013 [53] Mueller et al., 2018 [54]	Eigenvector centrality	24 PD patients	Increased functional connectivity between cerebellum and thalamus, putamen, globus pallidus, and brainstem in PD after levodopa intake compared to OFF state
Esposito et al., 2013 [44]	ICA-based and fALFF analyses (SMN)	20 early PD vs18 HC	Decreased connectivity within the SMA in PD compared to HC. Levodopa increases SMN connectivity
Rolinski et al., 2015 [38]	ICA-based analysis (BGN)	32 early PD vs 19 HC vs 31 AD	Decreased connectivity within the BGN in PD compared to AD and HC with the greatest change seen in the posterior putamen
Tessitore et al., 2012 [61]	ICA-based analysis (DMN, FPN, SN)	29 PD (16 with vs 13 without FOG) vs 15 HC	Decreased functional connectivity in the right occipito-temporal gyrus within FPN and VS in PD with FOG compared to those without
Fling et al., 2014 [62]	Seed-based analysis (SMA, STN, mesencephalic and cerebellar locomotor regions)	15 PD (8 with vs 7 without FOG) vs 14 HC	Increased functional connectivity between the SMA and mesencephalic as well as cerebellar motor regions in PD with FOG compared to those without and HC
Canu et al., 2015 [63]	ICA-based analysis (SMN, DM, VN, SN, and right FPN)	53 PD (28 with vs 25 without FOG) vs 35 HC	Decreased functional connectivity in the M1 and SMA within the SMN as well as in frontoparietal regions within the DMN, and occipital cortex within the VS in PD with FOG compared to HC
Chen et al., 2015 [57]	ALFF analysis	31 PD (12 TD vs 19 PIGD) vs 22 HC	Increased connectivity in the right cerebellar posterior lobe in TD compared to HC as well as decreased connectivity in the putamen and cerebellar posterior in PIGD compared to HC. Increased connectivity in the bilateral putamen and the cerebellar posterior lobe, as well as decreased connectivity in the bilateral temporal gyrus and the left superior parietal lobule in TD compared to PIGD
Karunanayaka et al., 2016 [58]	ICA-based analysis (DMN); ALFF analysis	17 akinetic PD vs 15 TD vs 24 HC	Decreased connectivity in the left inferior parietal cortex and the left posterior cingulate cortex within the DMN in akinetic PD compared to HC and TD

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Ma et al., 2017 [29]	Graph-analysis	31 PD (12 TD vs 19 PIGD) vs 22 HC	Decreased connectivity in the basal ganglia, cerebellum, superior temporal gyrus, pre- and postcentral gyri, inferior frontal gyrus, middle temporal gyrus, lingual gyrus, insula, and parahippocampal gyrus in PD compared to HC. PIGD had more disrupted hubs in the cerebellum than the TD.
Premotor phase and non-motor symptoms correlates			
Rolinski et al., 2016 [40]	ICA-based analysis (BGN)	26 iRBD vs 48 PD vs 23 HC	BGN connectivity of differentiated iRBD and PD from HC. No difference between iRBD and PD
Olde Dubbelink et al., 2014 [98]	Seed-based analysis (92 ROI covering the entire brain)	55 PD vs 15 HC	Progressive connectivity deterioration in precentral gyrus, postcentral gyrus, superior, middle, and inferior occipital gyrus, calcarine cortex, cuneus, and superior temporal gyrus over 3 years in PD patients
Tessitore et al., 2012 [97]	ICA-based analysis (DMN)	16 PD vs 16 HC	Decreased connectivity in the right medial temporal lobe and bilateral inferior parietal cortex within the DMN in PD compared to HC
Amboni et al., 2015 [99]	ICA-based analysis (DMN, FPN, VN)	42 PD (21 with and 21 without MCI) vs 20 HC	Decreased connectivity in bilateral prefrontal cortex within the FPN in PD with MCI compared to HC
Baggio et al., 2015 [104]	ICA-based connectivity (DMN, DAN, FPN)	65 PD (34 with and 31 without MCI) vs 38 HC	Decreased connectivity between DAN and right frontoinsular regions in PD with MCI compared to HC. Increased connectivity between DMN and medial and lateral occipito-parietal regions in PD with MCI compared to HC. Decreased DAN-DAN, DMN-DMN and DAN-FPN connectivity, as well as loss of normal DAN-DMN anticorrelation in PD with MCI compared to HC
Chen et al., 2015 [103]	Seed-based analysis (bilateral PCC)	30 PD (11 with and 19 without dementia) vs 21 HC	Decreased posterior cingulate cortex connectivity with the right medial temporal lobe in PD compared to HC. Decreased posterior cingulate cortex connectivity with right parahippocampal region in PD with dementia compared to those without
Putcha et al., 2015 [21]	ICA-based analysis (DMN, CEN, SN)	24 PD patients vs 20 HC	Decreased SN–CEN coupling and increased DMN–CEN coupling in PD compared to HC
Díez-Cirarda et al., 2018 [100]	ICA-based analysis (subcortical, AN, SMN, VN, cognitive-control, DMN and cerebellar network); graph-analysis	35 PD (23 with and 12 without MCI) vs 26 HC	Decreased dynamic connectivity in PD with MCI compared to HC. Decreased inter-network connectivity between the SMN-central control, SMN-VN, SMN-AN, central-control-VN and subcortical-DMN in PD with MCI compared to HC
Zhan et al., 2018 [101]	Seed-based analysis (bilateral posterior cingulate cortex)	27 PD (9 with and 9 without MCI vs 9 with dementia) vs 9 HC	Increased posterior cingulate cortex connectivity in PD with MCI patients and decreased posterior cingulate cortex connectivity in PD with dementia compared to HC. Increased connectivity between prefrontal cortices and posterior cerebellum in PD with dementia compared to HC

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Lopes et al., 2017 [26]	Graph-analysis	119 PD patients (31 cognitively unimpaired vs 31 with slight mental slowing vs 43 with mild to moderate deficits mainly in executive functions vs 14 patients with severe deficits in all cognitive domains	Functional organization decreased as cognitive impairment worsened. Between-group differences in functional connectivity mainly within the ventral prefrontal, parietal, temporal and occipital cortices as well as the basal ganglia
Skidmore et al., 2013 [90]	ALFF analysis	15 PD	Apathy severity is correlated with connectivity in the left supplementary motor cortex, the right orbitofrontal cortex, and the right middle frontal cortex. Depression severity is correlated with connectivity in the right subgenual cingulate
Baggio et al., 2015 [89]	Seed-based analysis (limbic, executive, rostral motor, and caudal motor regions)	62 PD (25 with vs 37 without apathy) vs 31 HC	Decreased connectivity in limbic striatal and frontal regions in PD patients with apathy compared to those without and HC
Tessitore et al., 2016 [92]	ICA-based analysis (DMN, FPN, SN, SMN, VS, AN)	40 PD (20 with vs 20 without distressing fatigue) vs 20 HC	Decreased connectivity in the SMA within the SMN as well as increased connectivity in the prefrontal and posterior cingulate cortices within the DMN in PD patients with fatigue compared to those without
Su et al., 2015 [80]	ReHo analysis (left rectal gyrus, orbitofrontal cortex, superior temporal pole, posterior cingulate cortex, right insula, amygdala)	54 PD (38 with vs 16 without hyposmia) vs 22 HC	Decreased connectivity in olfactory regions (i.e., amygdala, olfactory gyrus, orbital frontal cortex, parahippocampal gyrus and insula) as well as increased connectivity in the left anterior/posterior cingulate cortex in PD with hyposmia compared to those without
Yoneyama et al., 2018 [81]	ICA-based (CEN, DMN, SN, VN) and seed-based analysis (amygdala)	30 PD (15 with and 15 without hyposmia) vs 15 HC	Decreased connectivity between amygdala and olfactory cortices in PD with hyposmia compared to HC; increased connectivity within the CEN, SN and VN in PD patients with hyposmia compared to HC
Wen et al., 2013 [84]	ALFF analysis	33 PD (17 with vs 16 without depression) vs 21 HC	Decreased connectivity in the DLPFC, ventromedial prefrontal and the rostral anterior cingulated cortices in PD with depression compared to those without
Sheng et al., 2014 [87]	ReHo analysis (left middle frontal gyrus, right inferior frontal gyrus, left amygdala and bilateral lingual gyrus)	41 PD (20 with vs 21 without depression) vs 25 HC	Increased connectivity in the left middle frontal gyrus and right inferior frontal gyrus as well as decreased connectivity in the left amygdala and bilateral lingual gyrus in PD with depression compared to those without
Lou et al., 2015 [83]	Eigenvector centrality	34 PD (17 with vs 17 without depression) vs 17 HC	Decreased connectivity in the left DLPFC and right superior temporal gyrus as well as increased connectivity in the right posterior cingulate cortex, in PD with depression compared to those without
Hu et al., 2015 [88]	Seed-based analysis (amygdala)	60 PD (20 with vs 40 without depression) vs 43 HC	Increased connectivity between left amygdala and bilateral mediodorsal thalamus as well as increased connectivity between right amygdala and left superior temporal gyrus and left calcarine gyrus in PD with depression compared to those without

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Levodopa-induced dyskinesias			
Cerasa et al., 2015 106]	Seed-based analysis (right inferior frontal cortex)	24 PD (12 with vs 12 without LID)	Decreased connectivity of the right inferior frontal cortex with the left motor cortex as well as increased connectivity with the right putamen in PD with LID compared to those without
Herz et al., 2016 [107]	Seed-based analysis (bilateral putamen, M1, SMA and preSMA, right inferior frontal cortex)	24 PD (12 with vs 12 without LID)	Dopaminergic modulation of connectivity between the putamen and primary sensorimotor cortex predicted LID development with a specificity of 100% and a sensitivity of 91%

PD, Parkinson's disease; AD, Alzheimer's disease; HC, healthy controls; DMN, default-mode network; FPN, frontoparietal network; SN, salience network; CEN, central executive network; DAN, dorsal attention network; SMN, sensorimotor network; VN, visual network; AN: auditory network; BGN, basal ganglia network; ICA, independent component analysis; ALFF, amplitude of the low frequency fluctuations; ReHo, regional homogeneity; ROI, region of interest; STN, subthalamic nucleus; SMA, supplementary motor area; M1, primary motor cortex; DLPFC, dorsolateral prefrontal cortex; TD, tremor-dominant; PIGD, postural instability and gait difficulty; FOG, freezing of gait; MCI, mild cognitive impairment; LID, levodopa-induced dyskinesias; iRBD, idiopathic REM behavioral disorders.

DIAGNOSIS OF PD AND MOTOR SYMPTOMS CORRELATES

Paralleling the neuropathological progression of PD, RS-fMRI changes (both increase and decrease functional connectivity) involving the dopaminergic cortico-striatal and mesolimbic-striatal loops have been consistently detected in PD patients [20], providing a valuable contribution to the comprehension of the pathopsysiological mechanisms underlying motor symptoms in PD.

A recent meta-analysis [36], revealed that a decreased functional connectivity within the posterior putamen is the most consistent finding across different RS-fMRI studies in PD patients, with a progressive correlation with symptoms severity. This subcortical area and its cortical projections are engaged in a functional network which has been shown to be modulated by levodopa administration [36, 37].

A method to map functional connectivity within the basal ganglia (i.e., basal ganglia network, BGN) has been developed using a BGN template derived from 80 elderly controls [38, 39]. Patients with PD showed a reduced functional connectivity in a wide range of BGN areas (such as putamen, caudate, anterior thalamus, dorsolateral prefrontal cortex and precuneus). Average BGN connectivity was able to differentiate patients with PD from controls with 100% sensitivity and 89.5% specificity [39]. However, in a following study [40] the BGN connectivity was not able to differentiate subjects with idiopathic REM sleep behavior disorder (iRBD) from PD

patients, thereby limiting the potential role of this network as a diagnostic biomarker in PD patients (more details below).

At a cortical level, a decreased functional connectivity within the SMA, a cortical area linked to motor preparation and initiation [41], has been consistently found in PD patients compared to healthy controls at different disease stages [42–46]. Some studies also demonstrated an increased RS functional connectivity within the primary motor cortex (M1) in PD patients [43]. Even though decreased connectivity may be straightforward associated to loss of neural function, it is important to note that increased connectivity has also pathologic connotations. First, increased connectivity may be compensatory, representing a network response to local neuronal injury that allows for the maintenance of the same global performance. Second, what we see as "hyperconnected" may be underlined by the loss of networks dynamic properties to shift between different states (i.e., from a "hyper-" to a "hypo-connected" state).

In a cohort of drug-naïve PD patients, we performed an ICA-based RS-fMRI study and demonstrated the presence of specific SMN connectivity changes when compared to healthy controls, which were partially restored by the first levodopa administration [44]. Moreover, a ROI analysis of the SMN functional connectivity within the basal ganglia and thalamus revealed that levodopa significantly increases the participation of these subcortical regions to the SMN activity. This is consistent with several studies showing a specific levodopa modulation of the cortico-striatal functional connec-

tivity occurring in parallel with motor symptoms improvement [36, 37].

Interestingly, no statistically significant connectivity changes were detected in drug-naïve PD patients compared to controls within the M1, confirming that the compensatory functional reorganization of this area, previously reported, may be related to a prolonged dopaminergic treatment rather than to PD per se [44]. Moreover, in the same report no grey matter atrophy was detected in PD patients, suggesting that functional connectivity abnormalities may arise even before brain structural changes become evident. This suggests that RS-fMRI may be used as a biomarker of early cortical-subcortical functional aberrant phenomena potentially following initial neuropathological PD-related changes.

In this framework, it is interesting that SMN connectivity abnormalities in the absence of structural changes were also detected in asymptomatic LRRK2 (G2019S) mutation carriers, suggesting that functional changes may occur also during the preclinical phase of the disease (see below for further details) [47, 48].

In summary, functional connectivity changes involving the cortico-striatal pathway have been consistently shown in PD patients, with a clinical correlation with symptoms severity and a specific sensitivity to levodopa stimulation, suggesting that: 1) functional disruption within this network and all across its hubs may be considered as a correlate of the neuropathological process underlying PD and symptoms development, 2) this functional architecture may be potentially used as a biomarker of treatment response throughout the disease course.

Longitudinal studies are warranted to support this hypothesis. Along this research line, Manza and colleagues [49] seeded the striatum and its subdivisions in a cohort of early PD patients to characterize the pattern of functional disconnection occurring over 1 year. Their data revealed that motor symptoms progression is related to an increasing functional decoupling between anterior putamen and midbrain. This is consistent with previous findings in advanced PD patients also exhibiting a functional decoupling between striatum and midbrain regions when compared to controls [50], further supporting the role of RS-fMRI to mark disease progression of PD.

Another longitudinal study showed that an increased connectivity between cerebellum and the sensorimotor cortex is present at baseline and parallels with motor outcome deterioration in a cohort of early PD patients at 1.5-year follow-up [51]. Previous reports revealed an increased connectivity within the cerebellum in PD patients compared to controls [43, 52] as well as an impaired functional communication between cerebellum and other SMN areas [52]. This pattern has been interpreted as compensatory, but it should be noted that the role of chronic dopaminergic treatment has been also involved in the development of aberrant functional connectivity response within the cerebellum [53, 54].

In summary, at this point functional connectivity changes within the cerebellum may potentially support the clinical diagnosis of PD but they cannot be considered as a reliable biomarker to track PD progression over time.

Changes within non-motor RSNs and areas have been also found in PD patients compared to controls. Indeed, a recent meta-analysis merging RS-fMRI data from 854 PD patients and 831 controls, found that an increased functional connectivity within the post-central gyrus is the most consistent finding across studies, with a cross-validation in an independent dataset [55]. Similarly, another meta-analysis found convergent evidence for intrinsic functional disturbances in bilateral inferior parietal lobule in PD patients compared to healthy controls [56]. The potential role of the parietal cortex to monitor disease progression is suggested in a graph-analysis study, wherein topological global and nodal feature of the functional connectome were extracted in a large cohort of PD patients, across different disease stages [27]. This study showed that the nodal centralities in the left post-central gyrus were correlated with motor outcome and progressed along with disease stage [28].

Non-motor RSNs changes were also revealed by comparing different PD motor phenotypes. Indeed, a decreased functional connectivity within the DMN has been revealed in cognitively unimpaired akinetic-dominant PD patients compared to both tremor dominant patients and controls [57, 58], confirming that different motor phenotypes may be related to a distinctive underlying pathophysiology, coupled with a divergent risk profile for the development of cognitive impairment [59, 60]. In this framework, the presence of freezing of gait, which is considered a clinical biomarker of worse disease progression and earlier development of cognitive impairment, has been consistently associated with specific involvement of cognition and attention-related RSNs, encompassing frontal, parietal and temporo-occipital areas [61–63].

PREMOTOR PHASE AND NON-MOTOR SYMPTOMS CORRELATES

As neuroprotective treatment in early stages could prevent clinical PD from emerging, in the last years a great deal of effort has been gone in the identification of clinical and pre-clinical aspects, timing and risk of PD development. To this aim, a dedicated Task Force of The International Parkinson and Movement Disorder Society, has released proposed criteria for prodromal PD [2]. However, to date only a few studies have been focused on RS-fMRI signatures of subjects at clear risk to develop PD.

RBD is characterized by loss of the normal atonia during REM sleep [64]. RBD has shown an incomparable potential as a prodromal PD marker, with an estimated period of 10–15 years of progressive neuronal loss before the onset of the core motor symptoms [65]. Therefore, in the last years several studies have investigated neural correlates of iRBD with a high risk of progression in PD [66–71]. A few studies have addressed functional connectivity changes in patients with iRBD. The first one [72], using a seed-based approach, has revealed an altered nigrostriatal connectivity pattern in patients with iRBD. A more recent one [40], has shown that BGN connectivity measures may differentiate both iRBD and PD from controls. These results clearly demonstrate that a disrupted functional connectivity within motor regions may be detected in iRBD even before the development of motor symptoms. However, it is important to note that in the same study 123I-ioflupane single photon emission computerized tomography was able to differentiate iRBD from PD patients whereas BGN connectivity did not, and this could limit the robustness of findings [40].

Healthy carriers of the G2019S LRRK2 mutation represent an interesting human model of premotor PD. Indeed, PD LRRK2 parkinsonism is associated with Lewy body pathology and with similar clinical signs as idiopathic PD [73]. Presence of LRRK2 G2019S mutation is associated with a markedly increased, age-dependent risk of developing PD [73] with a penetrance estimations ranging from 10%–17% at the age 50 years to 25%–85% at the age of 70 years [73]. Recently, a seed-based RS-fMRI study revealed that the right inferior parietal cortex had a reduced connectivity with the posterior putamen and an increased connectivity with the anterior putamen in LRRK2 G2019S mutation carriers compared with noncarriers [47]. Similarly, in early-stage PD patients, presence of a shift in corti-costriatal connectivity from severely affected striatal regions (posterior putamen) to less affected striatal regions (anterior putamen) with a potential compensatory role has been highlighted [49]. More recently, asymptomatic LRRK2 mutation carriers showed RS functional connectivity changes in striatocortical and nigrocortical circuits compared with noncarriers [48]. These findings support the concept that an altered cortico-nigro-striatal connectivity may precedes clinical symptoms onset, at least in genetic forms of PD, and may be potentially proposed as a early biomarker of the neurodegeneration process leading to PD development.

Evidence from neuropathological studies [74, 75] have shown that noradrenergic, serotonergic and cholinergic pathways are severely affected by neurodegenerative processes during the prodromal stage of PD, prior to *substantia nigra* degeneration [75]. Alteration of non-dopaminergic pathways has been detected as an underlying correlate of several non-motor symptoms in PD, which may characterize the prodromal disease stage. Thus, functional connectivity correlates of non-motor symptoms, even when studied in patients with a clinical diagnosis of PD, may provide interesting suggestions about early disease spreading processes and pathways to be targeted with novel treatments.

Hyposmia is a well-established and early non-motor symptom of PD [76, 77]. Several studies have suggested its role as a potential biomarker of PD progression and cognitive decline [79]. To date, only a few studies have assessed neural correlates of hyposmia in PD patients [80, 81]. In one study [80] PD patients with hyposmia, compared with those without hyposmia, showed a decreased functional connectivity within both olfactory and non-olfactory related cortical areas and an increased functional connectivity in the left anterior/posterior cingulate cortex, with a potential PD-pathology-related compensatory role. A more recent study [81] showed that hyposmia is associated with a decreased functional connectivity within the limbic/paralimbic system and between amygdala and parietal/occipital areas, which was correlated with hyposmia severity.

Depression in PD may be considered as an interface between emotional processing and cognitive functions [82]. Indeed, using different RS-fMRI approaches, an intrinsic dysfunction within the dorsolateral prefrontal cortex in depressed PD (dPD) patients has been observed [83, 84]. This cortical area has a pivotal role in the prefrontal-limbic network, and is also involved in cognition and executive

functions [85, 86]. Moreover, two RS-fMRI studies has emphasized the role of the amygdala in mood modulation, revealing an abnormal connectivity within this area in dPD patients [87, 88]. Whereas, the presence of apathy in PD has been associated with a disrupted functional connectivity in frontostriatal pathways [89, 90], mainly involving its limbic components. Fatigue is a common and disabling non-motor symptom in PD patients [91]. A recent RS-fMRI study [92] has revealed that fatigue is associated with a divergent pattern of functional connectivity within SMN and DMN in drug-naïve PD patients. Moreover, fatigue severity was correlated with these connectivity changes, suggesting that an efficient functional interplay between these cortical areas might be necessary to maintain a good motor performance without development of fatigue.

In recent years, an intrinsic aberrant functional connectivity within the DMN has been implicated in cognitive processing in several neurodegenerative disorders [93–95]. A recent meta-analysis showed that decreased functional connectivity within the DMN is the most consistent finding able to differentiate PD patients with and without cognitive impairment [96]. In a cohort of early-stage cognitively unimpaired patients with PD, we demonstrated the presence of a decreased medial temporal and inferior parietal connectivity within the DMN, which was correlated with cognitive performances [97]. This finding suggests that functional disconnection of posterior brain regions can precede clinically measurable cognitive impairment in PD. Interestingly, functional connectivity deterioration in posterior cortical regions has been associated with progression of cognitive impairment over 3 years in a longitudinal fMRI study [98]. Moreover, alterations within the DMN have been shown to be more relevant in PD patients with MCI [99–101] and with dementia [97, 101–103], further supporting the potential role of RS-fMRI to depict a sensitive and specific biomarker of dementia in PD for prognostic and disease-monitoring purposes.

Together with the DMN, other important neurocognitive RSNs have been found to be correlated with cognitive deficits in PD, such as the DAN, CEN, SN and associate visual networks [21, 98, 99, 104] and an efficient inter-network connectivity between these networks is relevant, as well [21, 22]. This is consistent with the hypothesis that two different patterns of cognitive impairment may generally occur in patients with PD: an anterior, frontostriatal executive syndrome, more common in early disease and

with a low rate of evolution in dementia, and a more posterior cortical syndrome, which has been related to worse cognitive prognosis over time [105]. In this framework, application of RS-fMRI measures may allow to detect those patients early presenting with a functional architecture more frequently associated with cognitive impairment and stratify the risk of developing dementia over time.

LEVODOPA-INDUCED DYSKINESIAS

LID represents a major debilitating side effect of long-term DRT in PD. To date, these complications have been assessed by means of fMRI task-based studies [6]. Only two studies focused on intrinsic functional connectivity correlates of LID [106, 107]. In details, functional connectivity was assessed in a RS-fMRI study centering the right inferior frontal cortex, a cortical area critically involved in motor control and inhibition, in PD patients with LID compared with those without [106]. The study revealed that connectivity of the right inferior frontal cortex is decreased with the left motor cortex and increased with the right putamen in patients with LID when switching from the OFF to the ON phase of levodopa treatment. Moreover, the degree of such alteration correlated with motor disability. Interestingly, the Authors performed an additional and independent experiment, applying different forms of repetitive transcranial magnetic stimulation over the right inferior frontal cortex in a new group of dyskinetic PD patients who were taking a supramaximal dose of levodopa, which were able to reduce the amount of hyperkinetic movements [106]. Together with evidence from other task-based fMRI as well as corticometric studies [108], this study suggests that this area may play a key role in controlling the development of LID. These data were not confirmed in a more recent study by Herz and coll. [107], which analyzed levodopa-induced modulation of cortico-striatal resting-state connectivity between the putamen and three cortical ROIs: SMA, primary sensorimotor cortex, and right inferior frontal gyrus. Indeed, no interaction has been found between modulation of the right inferior frontal gyrus/putamen connectivity and LID development and severity. However, dopaminergic modulation of RS connectivity between the putamen and primary sensorimotor cortex in the most affected hemisphere predicted whether patients would develop LID with a specificity of 100% and a sensitivity of 91%. Moreover,

the levodopa modulation of RS connectivity between the SMA and putamen was able to predict LID severity. These apparently divergent results may stem from methodological and design discrepancies between the two studies. Nevertheless, both these studies suggest that levodopa intake may interfere with the physiological organization of the cortico-putaminal connectivity in LID patients. However, it is not yet clear whether this network reorganization is related to chronic DRT or may be considered as a premorbid pattern predisposing to LID development. Prospective and longitudinal studies are still lacking and should be specifically designed to determine the role of RS-fMRI to predict LID development over time.

CONCLUSION

Overall, RS-fMRI literature supports that an aberrant functional interplay within corticostriatal loops may characterize PD patients from controls. These functional abnormalities have been detected both in the early stage of the disease and in subjects at high risk to develop clinical established PD and may be potentially proposed as early biomarkers to track PD-related neurodegeneration pathway. Moreover, a few studies comparing different PD stages and applying longitudinal designs showed potential compensatory effects and treatment-related changes which may arise throughout the disease progression, and also detected intrinsic brain connectivity signatures to be targeted for prediction and neuroprotection purposes. However, development of reproducible and clinically useful RS-fMRI imaging biomarkers of PD is needed to overcome some inconsistencies between studies, mainly related to the complexity of the disease.

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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