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Alterations in Large-Scale Intrinsic Connectivity Networks in the Parkinson's Disease-Associated Cognitive Impairment Continuum: A Systematic Review

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ABSTRACT

Introduction: Cognitive impairment is common in the course of Parkinson's disease (PD) and displays a continuum from subjective cognitive impairment to dementia. Illuminating the pathophysiological processes associated with the continuum may help create follow-up and new treatment approaches. In this context, large-scale intrinsic connectivity networks are widely investigated to elucidate the neural processes underlying PD and are promising as non-invasive biomarkers. This systematic review aims to examine the alterations in large-scale intrinsic connectivity networks in the continuum of PD-associated cognitive impairment.

Method: ScienceDirect, Web of Science, and PubMed databases were searched with the specified keywords. The studies obtained as a result of this review were investigated by the PRISMA criteria, which were taken as a basis for the systematic review and writing of meta-analyses.

Results: A total of 974 studies were obtained from three databases. Twenty studies were included in the systematic review based on predetermined eligibility criteria. Among the large-scale connectivity networks examined in these studies, it was found that sensory-motor networks decreased their connectivity in the continuum of PD-associated cognitive impairment, and there were conflicting results in terms of cognitive networks.

Conclusion: Well-designed longitudinal studies are needed to clarify the alterations in the intrinsic connectivity networks in the PD cognitive impairment continuum. In these studies, it is necessary to define the cognitive disorder groups well, to control the connectivity changes that may occur due to dopaminergic treatment, and to evaluate Parkinson's patients with subjective cognitive impairment and dementia within the continuum.

Keywords: Functional magnetic resonance imaging, intrinsic connectivity networks, Parkinson's disease, Parkinson's disease dementia, Parkinson's disease with mild cognitive impairment, resting-state networks

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INTRODUCTION

The current opinion on brain functions is based on representing various information domains in segregated neural communities and integrating pieces of information through dynamic interactions between circuits at multiple spatial scales of the central nervous system. This view derives from a wide variety of studies based on measurement techniques applied at various spatial scales of the organization of the nervous system organization, ranging from submicroscopic scale of molecular events and the microscopic scale of single-cell recordings to the mesoscopic scale of interaction within local-scale neuronal ensembles and the macroscopic scale of large-scale brain networks. The common point of all previous studies conducted based on the spatial scales mentioned above is that they are either carried out to inspect the development and change of the brain in healthy people or to elucidate the pathogenetic processes of various neuropsychiatric diseases. Regarding neuropsychiatric diseases, one of the most studied subjects is cognitive disorders. Recent studies on cognition have increasingly focused on the network paradigm (1). This paradigm postulates that cognitive functions arise from the collaborative work of distributed and interconnected brain systems organized into large-scale networks (2).

In this context, functional magnetic resonance imaging (fMRI) has been the most widely used method for examining large-scale brain networks (3). fMRI is the recording of brain activity based on changes in the level of cerebral blood oxygenation. There are two main areas where information about how the brain works can be obtained by examining brain activity. The first is localization, which tries to associate certain brain areas with specific functions. Many researchers use behavioral tasks that participants perform in fMRI to localize functionally specialized regions of the brain that are activated in response to a particular aspect of behavior, and task-related activation is localized by measuring blood oxygenation level-dependent (BOLD) signal across different conditions (4).

Another approach used to study brain activity is connectivity imaging, which explores how brain regions communicate and how information is

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Highlights

- **Cognitive impairment (CI) is common and continuous in Parkinson's disease (PD).**
- **fMRI is widely used in PD-associated CI research.**
- **The connectivity of sensory-motor networks is decreased in PD-associated CI.**
- **There are conflicting results in the connectivity of congitive networks in the PD-associated CI.**
- **Longitudinal stuides are required to use intrinsic connectivity networks (ICNs) as biomarkers in the PD-associated CI.**

transferred from one brain area to another. Connectivity neuroimaging is categorized as structural imaging and functional imaging. In structural connectivity neuroimaging, diffusion tensor imaging (DTI) and methods derived from it display axonal connectivity pathways. In contrast, functional connectivity neuroimaging displays low-frequency BOLD signal fluctuations (0.01-0.1 Hz) that show a high degree of synchronization at rest in brain regions that are spatially distant from each other. These fluctuations are components of functional intrinsic connectivity networks (ICNs) (5–7).

These fluctuations can be analyzed as hypothesis-driven or data-driven fluctuations (8). The hypothesis-driven approach investigates changes in the connectivity of a pre-selected brain region or regions, called the seed, with other brain regions. These examinations can be in the form of investigating the connectivity of the selected seed with other anatomically or functionally bound seeds (seed-to-seed) or determining the connectivity of the voxels in the whole brain (seed-to-voxel). Data-driven approaches attempt to identify consistent spatial fluctuation patterns in the BOLD signal. In this context, the most used data-driven analysis method is independent component analysis (ICA). ICA splits the BOLD signal into independent components represented by three-dimensional spatial maps and a corresponding time series. While these components may have a neural basis, head movement or physiological noises may also appear as other components (9). Neural components, namely ICNs, show a spatial pattern consistent with brain regions activated during cognitive tasks. These spatial similarities were considered when naming these networks (Figure 1). Because ICNs are highly consistent and reproducible both within and between participants, they have the potential as a non-invasive biomarker by revealing the neural processes underlying various neuropsychiatric diseases (1,7)

Parkinson's Disease-Associated Cognitive Impairment

In Parkinson's disease (PD), which is diagnosed with conventional motor findings, the counterpart of these findings is neurodegeneration, represented by the loss of dopaminergic neurons in the substantia nigra pars compacta (10–12). Nigrostriatal dopaminergic deafferentation leads to motor symptoms of the disease. However, considering the caudo-rostral progression of the disease from the lower brain stem, the motor symptoms elicited by the involvement of nigral dopaminergic neurons correspond to the middle stage of the disease. Although the diagnostic criteria consist of motor findings, it is understood that non-motor symptoms such as chronic constipation, depression, anxiety, parasomnia, and hyposmia can be seen years before motor symptoms appear with the involvement of the lower brain stem and the olfactory bulb (13). One essential non-motor manifestation of PD is cognitive impairment, which is seen up to 6 times more frequently in the course of PD than in normal population (14).

Although the spectrum of cognitive impairment associated with PD is often defined as a continuum extending from PD with mild cognitive impairment (PD-MCI) to PD dementia (PD-D), it is known that approximately 39% of newly diagnosed PD patients also have subjective cognitive impairment (PD-SCI) (15). SCI represents an individually perceived decline in cognitive ability even though the patient normally performs on standardized cognitive tests and is not associated with an acute event (16).

In contrast, PD-MCI refers to the non-functional decline in cognitive ability reported by the patient or patient's relatives or observed by the clinician. For the diagnosis of PD-MCI, the Movement Disorder Society (MDS) has proposed a two-stage operational scheme. According to this scheme, in the Stage I criteria, impairment in a proposed global cognitive screening test or impairment in at least two neuropsychological tests when a limited number of tests are used to measure cognition leads to diagnosis of PD-MCI (17,18). According to Stage II criteria, PD-MCI is diagnosed, when 1-2 standard deviations below the norm in one of the five cognitive domains (attention and working memory, executive functions, language, memory, and visuospatial functions) evaluated with at least two neuropsychological tests or in one test in two different cognitive domains (17). MDS criteria may introduce some variability due to lack of specificity regarding cutoff points for impairment in neuropsychological testing. Within this framework, the most recent studies use a threshold value of 1.5 for standard deviations below the normative means of tests (19). PD-MCI can be classified into single or multiple domains, depending on the number of cognitive domains affected. If there is deterioration in two or more tests in one cognitive domain, the PD-MCI is classified as a single domain, while if there is impairment in at least one test in each of the two or more cognitive domains, it is classified as multiple domain (17).

Two phenotypes of PD-MCI, "benign" for an executive disorder and "malign" for a visuospatial disorder, were also defined, and called the "dual syndrome hypothesis," according to which, dysfunction in the frontostriatal dopaminergic circuitry leads to executive dysfunction, and patients with this phenotype do not always progress to PD-D. The posterior cortical/visual-spatial phenotype, called malign due to cholinergic transmission changes, is a risk factor for PD-D (20–23).

The main feature of the PD-D criteria of MDS is an insidious decline in more than one cognitive area that is severe enough to impair daily living functions and lasts for at least six months (24). Notably, various neuropsychiatric manifestations such as apathy, depression, visual hallucinations, and psychosis may accompany PD-D. As in the diagnosis of PD-MCI, a two-stage system has been developed for the diagnosis of PD-D. According to Stage I PD-D criteria, PD develops before the onset of dementia after excluding major depression, delirium, and other abnormalities that may complicate the diagnosis, scoring below 26 on the Mini-Mental State Examination (MMSE), motor symptoms independently have cognitive deficits severe enough to affect daily life and have impairment in at least two of the four cognitive domains (months reversed or seven backward, lexical fluency or clock drawing, pentagon drawing, and three-word recall) on the MMSE required (24–26). Stage II evaluation, on the other hand, evaluates four areas: global cognitive efficiency, subcortico-frontal features of PD-D, instrumental (cortical-mediated) functions, and neuropsychiatric features (For detailed information, see. Dubois et al. 2007). Also, atrophy on cranial MRI is associated with PD-D; however, the pattern of regional atrophy is variable and can appear in any brain region (27–29).

Uncovering the neural mechanisms underlying the persistence of PD-associated cognitive impairment may be beneficial for the follow-up of the disease and for developing new treatment approaches. In this context, studies investigating resting-state functional connectivity in the framework

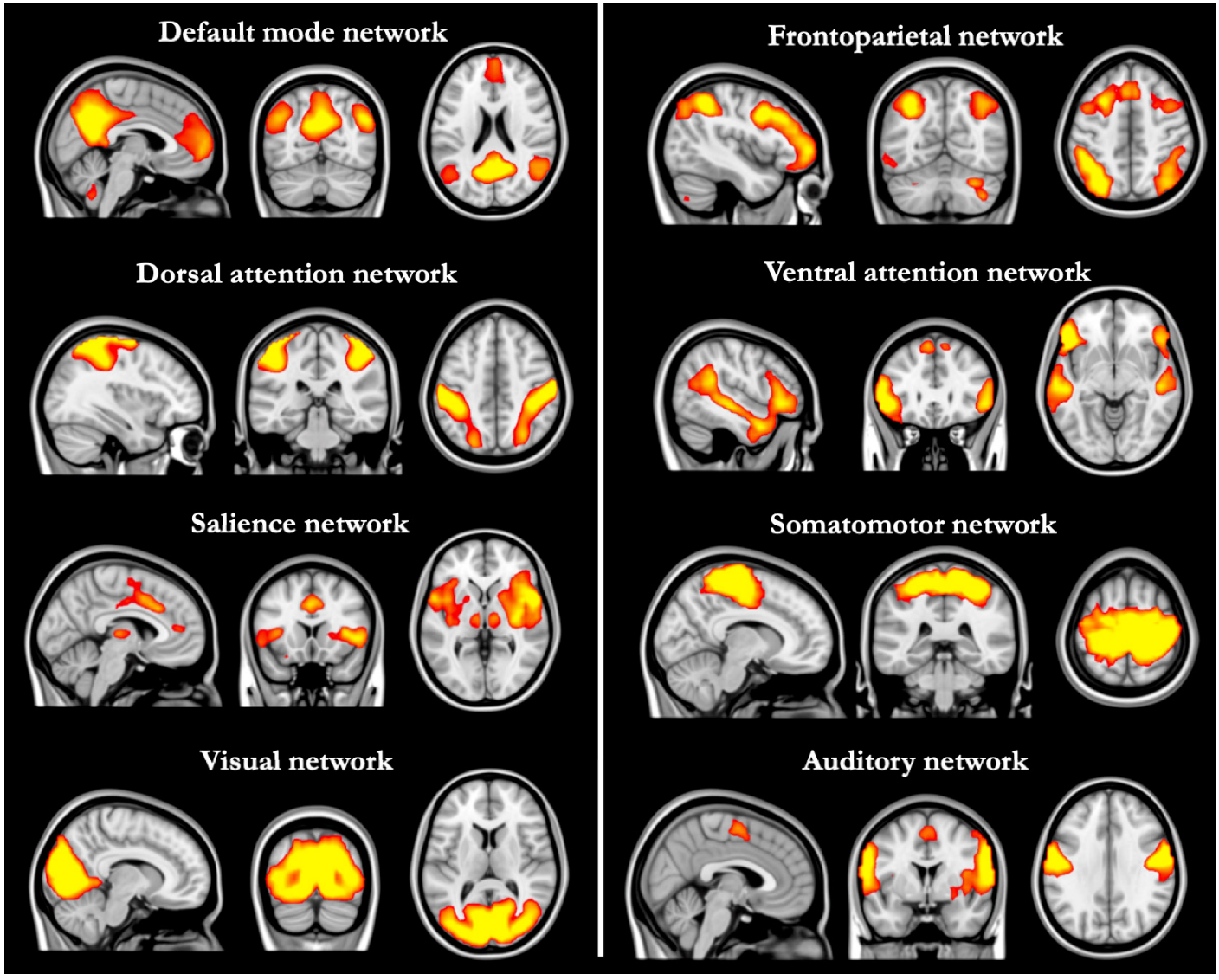


Figure 1. Large-scale intrinsic connectivity networks

of the network approach are increasing rapidly, and it is thought that these studies will also be vital in terms of the clinical effect of the disease. This systematic review aims to examine studies investigating changes in large-scale intrinsic connectivity networks in the continuum of PD-associated cognitive impairment ranging from normal cognition to dementia.

METHOD

This systematic review was conducted in line with PRISMA criteria, which were used to write systematic reviews and meta-analyses (30). First, a literature search was conducted in ScienceDirect, Web of Science, and PubMed databases, using search terms suitable for the systematic review (Table 1), covering the entire text (Last search date 18 April 2022). As a result, a total of 974 studies were accessed, of which 643 were in ScienceDirect, 224 were in Web of Science, and 107 in PubMed. Then, the titles and abstracts of these studies were reviewed, and the scanning phase was completed after the studies were removed because the same study appeared in all three databases (n=394), meeting abstracts (n=40), and the letter to the editor (n=5). The full texts of 535 articles were reviewed to examine the eligibility criteria. Eligibility criteria defined within the scope of this study: 1) The study should be a research or meta-analysis article; 2) Include at least one of the PD-MCI or PD-D groups that address the PD-associated cognitive impairment continuum (studies comparing healthy controls and the cognitively normal PD (PD-CN) group were not considered appropriate because they could not be evaluated in the cognitive impairment continuum); 3) Diagnosis of PD-associated cognitive disorder according to current criteria; and 4) Investigation of large-scale intrinsic connectivity networks based on the fMRI. As a result of the application of these criteria, 515 studies were excluded for different causes (Figure 2), and 20 studies were included in the systematic review.

RESULTS

The designs, samples, diagnostic criteria, analysis methods, and findings of the 20 studies by the eligibility criteria are summarized in Table 2. In this context, alterations in large-scale networks in the PD-associated cognitive impairment continuum will be discussed under separate headings.

Default Mode Network

The default mode network (DMN) consists of bilateral and symmetrical cortical regions, including the medial and lateral parietal cortex, medial prefrontal cortex, medial and lateral temporal cortices, and limbic components, covering the hippocampal formation and the amygdala (31). DMN is closely related to cognitive processes and plays an active

Table 1. Distribution of publications obtained as a result of database search with search terms

Search term	ScienceDirect	Web of Science	PubMed	Total
"Parkinson's Disease" AND ("cognitive impairment" OR "dementia") AND "Default Mode Network"	171	147	60	378
"Parkinson's Disease" AND ("cognitive impairment" OR "dementia") AND "Dorsal Attention Network"	58	10	8	76
"Parkinson's Disease" AND ("cognitive impairment" OR "dementia") AND "Ventral Attention Network"	33	3	4	40
"Parkinson's Disease" AND ("cognitive impairment" OR "dementia") AND "Visual Network"	46	7	4	57
"Parkinson's Disease" AND ("cognitive impairment" OR "dementia") AND ("Motor Network" OR "Somatomotor Network" OR "Sensorymotor Network" OR "Sensory-motor Network")	161	19	7	187
"Parkinson's Disease" AND ("cognitive impairment" OR "dementia") AND ("Frontoparietal Network" OR "Fronto-parietal Network" OR "Central Executive Network" OR "Central-executive Network" OR "Executive Control Network")	110	20	14	144
"Parkinson's Disease" AND ("cognitive impairment" OR "dementia") AND ("Salience Network" OR "Cingulo-opercular Network")	52	17	10	79
"Parkinson's Disease" AND ("cognitive impairment" OR "dementia") AND "Auditory Network"	12	1	0	13
Total	643	224	107	974

role in functions such as emotional processing, self-referential mental activity, and recall of previous experiences (31, 32). DMN has been the most researched ICN in PD and other neuropsychiatric disorders (1, 29). Amboni et al. (2015) found that connectivity of DMN structures, including the inferior parietal cortex, posterior cingulate cortex, and medial temporal lobe, did not differ between the PD-CN and PD-MCI groups (33). In contrast, PD-CN and PD-MCI groups had lower DMN connectivity than healthy controls (HCs). In another study, DMN connectivity in the PD-MCI group was lower than in PD-CN and HC (34).

Similarly, in a seed-based study conducted by Hou et al. (2016) in drug-naive, early-stage PD patients, it was found that PDs with cognitive impairment decreased the functional connectivity of region of interests (ROIs) of DMN with dorsal attention network (DAN) and frontoparietal network (FPN) compared to PD-CNs (35). They also showed that connectivity between the DMN (anterior temporal cortex) and the DAN (middle temporal gyrus) was positively correlated with attention and working memory scores. The connectivity within the DMN itself (between the hippocampus and the inferior temporal gyrus) was positively correlated with memory scores. While two studies (36, 37) suggested that intra-DMN connectivity decreased in the PD-MCI group compared to HC, however, without any difference between the PD-CN and PD-MCI groups; Kawabata et al. (2018) stated that the intra-DMN connectivity of PD patients with amnestic MCI (PD-aMCI) was found to decrease compared to both the non-amnestic PD-MCI (PD-naMCI) group and the PD-CN group. They also suggested that connectivity between the DMN and the cerebellar-brainstem network could correctly distinguish PD-aMCI and PD-naMCI at 86.4% with the support vector machine classification (38).

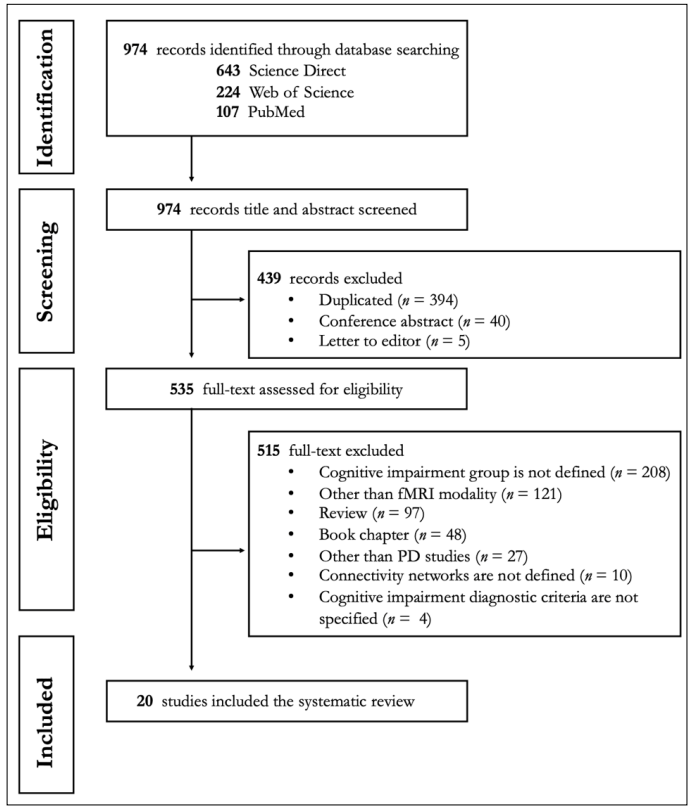


Figure 2. PRISMA flowchart for identification and eligibility of articles. n = number of articles

On the other hand, in the study of Chung et al. (2019), including PD-aMCI and PD-naMCI groups and HCs, there was no difference in terms of DMN connectivity between the two MCI groups, but when they compared the PD-MCI group as a single group and compared it with healthy controls, found that DMN showed bilaterally decreased connectivity of the entire cortex (39). In two studies using graph theory, Chen et al. (2020) showed increased nodal centrality in DMN in PD-MCI compared to PD-CN (40), and Hou et al. (2020) found decreased nodal centrality in newly diagnosed and drug-naive PD-MCI patients compared to HC (41). A meta-analysis of functional connectivity studies by Wolters et al. (2019), which included

Table 2. The designs, samples, diagnostic criteria, and summary findings of studies reviewed

Study (reference)	Design	Sample	Diagnostic criteria	Method	Results
Amboni et al. 2015 (33)	Cross-sectional	20 HC – 21 PD-CN – 21 PD-MCI	MDS Stage I	ICA	-Decreased DMN connectivity in PD-CN and PD-MCI than in HC -Decreased FPN connectivity in PD-MCI than PD-CN and PD-CDN than HC -Visuospatial functions, memory, and executive functions/ attention scores of the PD-CN and PD-MCI groups were positively correlated with FPN.
Baggio et al. 2015 (45)	Cross-sectional	36 HC – 43 PD-CN – 22 PD-MCI	MDS Stage I	ICA	-DMN-DAN and DMN-left FPN connectivity increased in PD-MCI compared to PD-CN and HC. This increased connectivity was negatively correlated with visuospatial scores. -In PD-MCI, intra-DAN and DAN-FPN connectivity decreased compared to PD-CN and HC. Decreased connectivity was positively associated with attention/executive function scores.
Gorges et al. 2015 (34)	Cross-sectional	22 HC – 17 PD-CN – 14 PD-MCI	MDS Stage I	ICA	-Decreased DMN, DAN, and SMN connectivity in PD-MCI than in both PD-CN and HC -Decreased VAN connectivity in PD-MCI than in PD-CN
Hou et al. 2016 (35)	Cross-sectional	22 HC – 18 PD-CN – 14 PD-MCI	MDS Stage II	SBA	-Decreased DMN and DAN-FPN connectivity in PD-MCI than in PD-CN -In all PD groups, DMN and DAN connectivity was positively correlated with attention/working memory score, and intra-DMN connectivity was positively correlated with memory score.
Pereza et al. 2017 (48)	Cross-sectional	30 HC – 62 PD-CN – 37 PD-MCI	MDS Stage II	ICA	-In PD-CN than HC, decreased DAN, SMN, and right FPN connectivity, increased left FPN connectivity -Decreased VN and DAN connectivity in PD-MCI than HC -Decreased FPN and VAN connectivity in PD-MCI than PD-CN
Bezdicek et al. 2018 (55)	Meta-analysis	30 HC – 15 PD-CN – 16 PD-MCI	MDS Stage II	MACM	-Altered connectivity between PD-MCI and PD-CN, especially in DAN and FPN
Diez-Cirarda et al. 2018 (36)	Cross-sectional	26 HC – 12 PD-CN – 23 PD-MCI	MDS Stage II	ICA, SBA	-Decreased DMN and thalamus connectivity in PD-MCI than HC -Decreased connectivity between FPN-SMN, FPN-VN SMN-VN, and SMN-AN in PD-MCI than HC
Kawabata et al. 2018 (38)	Cross-sectional	24 HC – 28 PD-CN – 20 PD-aMCI – 24 PD-naMCI	MDS Stage I	ICA	-The intra-DMN connectivity of PD-aMCI is lower than that of HC, PD-CN, and PD-naMCI -Connectivity between DMN and CBN correctly classified PD-aMCI and PD-naMCI with 86.4%
Aracil-Bolanos et al. 2019 (58)	Cross-sectional	34 PD-CN – 19 PD-MCI	MDS Stage I	SBA	-Intra-SN network coherence was higher in PD-CN than PD-MCI -Increased connectivity between DMN-SN in PD-MCI than PD-CN -SN node degree was positively correlated with global cognition and visuospatial scores; however negatively correlated with the TMT-B score
Chung et al. 2019 (39)	Cross-sectional	30 HC – 50 PD-aMCI – 50 PD-naMCI	MDS Stage II	SBA	-Decreased connectivity of DMN, FPN, and DAN in PD-MCI than HC, however, no connectivity difference between the two MCI groups. -Increased SN connectivity in PD-aMCI compared to both PD-naMCI and HC
Klobusiakova et al. 2019 (49)	Cross-sectional and longitudinal	51 HC – 17 PD-CN – 22 PD-MCI	MDS Stage II	SBA	-Decreased FPN-DMN, FPN-VN, and FPN-DAN connectivity in PD-CN compared to HC -Decreased FPN-VN connectivity in PD-CN compared to PD-MCI -Increased FPN-DMN and FPN-VN connectivity in the whole PD group after 1-year follow-up
Wolters et al. 2019 (42)	Meta-analysis	353 HC – 289 PD-CN – 222 PD-MCI – 68 PD-D	MDS Stage I and II	AES-SDM	-Decreased DMN, AN, and FPN connectivity in PD-MCI compared to HC -Decreased DMN connectivity in PD-MCI compared to PD-CN

Continuation of Table 2					
Arslan et al. 2020 (43)	Cross-sectional	15 HC – 26 PD-CN – 27 PD-MCI	MDS Stage I	ASL	-Hypoperfusion in FPN, in HC compared to PD-CN -Hypoperfusion in DMN, FPN, SMN, DAN and VN in PD-MCI compared to HC -SMN hypoperfusion in PD-MCI compared to PD-CN
Chen et al. 2020 (40)	Cross-sectional	18 HC – 45 PD-CN – 22 PD-MCI	MDS Stage I	SBA	-Decreased node centrality in SMN, increased node centrality in DMN, VN, and FPN in PD-MCI compared to PD-CN
Hou et al. 2020 (41)	Cross-sectional	28 HC – 19 PD-CN – 22 PD-MCI	MDS Stage II	SBA	-Decreased node centrality in DMN, FPN, and SMN, increased node centrality in VN and FPN in PD-MCI compared to HC
Azamat et al. 2021 (51)	Cross-sectional	17 PD-CN – 18 PD-MCI – 16 PD-D	MDS Stage I, MDS Task Force	ASL	-In PD-D; FPN and VN hypoperfusion compared to PD-MCI, PD-CN, and the merging of these two groups
Cascone et al. 2021 (50)	Cross-sectional	21 HC – 22 PD-CN – 37 PD-MCI	MDS Stage I	SBA	-The topological brain-network resilience of FPN is decreased in PD-MCI compared to PD-CN and HC
Hou et al. 2021 (37)	Cross-sectional	28 HC – 19 PD-CN – 28 PD-MCI	MDS Stage II	ICA	-Decreased connectivity in DMN, SMN, and VN in PD-MCI compared to HC -DMN connectivity was positively correlated with memory score, and VN connectivity was positively correlated with visuospatial functions score in the PD-MCI group -SMN and UPDRS-III scores are negatively correlated in all PD -Decreased connectivity between SMN-LN and between VAN-VN compared to HC in both PD-CN and PD-MCI
Ruppert et al. 2021 (46)	Cross-sectional	16 HC – 36 PD-CN – 12 PD-MCI	MDS Stage II	ICA, SBA	-Increased metabolic DMN connectivity in PD-CN and PD-MCI compared to HC -Both increased and decreased metabolic DMN connectivity between PD-CN and PD-MCI -Decreased DMN connectivity in PD-CN compared to HC whereas increased DMN connectivity in PD-MCI compared to both HC and PD-CN -General cognitive, visuospatial functions and attention scores and intra-DMN connectivity were negatively correlated, while executive functions score and intra-DMN connectivity were positively correlated
Schindlbeck et al. 2021 (44)	Cross-sectional	49 HC – 98 PD-CN – 45 PS-sMCI – 36 PD-mMCI – 19 PD-D	MDS Stage I, PD-D diagnosis: Dementia Rating Scale	ICA, SBA	-The expression scores of the DMN component, which includes the posterior cingulate cortex, cingulum, and thalamus, are decreased in PD-MCI compared to PD-CN -Ventral DMN expression scores are positively correlated with verbal recall scores

AES-SDM: Anisotropic effect size Seed-based d Mapping; aMCI: Amnestic mild cognitive impairment; AN: Auditory network; ASL: Arterial spin labeling; CBN: Cerebellar-brain stem network; DAN: Dorsal attention network; DMN: Default mode network; FPN: Frontoparietal network; HC: Healthy control; ICA: Independent component analysis; LN: Limbic network; MACM: Meta-analytic co-activation map; MCI: Mild cognitive impairment; MDS: Movement Disorders Society; mMCI: Multi-domain mild cognitive impairment; naMCI: Non-amnestic mild cognitive impairment; PD: Parkinson's disease; PD-CN: Cognitively normal PD; PD-D: PD with dementia; PD-MCI: PD with mild cognitive impairment; SBA: Seed-based analyses; sMCI: Single domain mild cognitive impairment; SMN: Somatomotor network; SN: Salience network; TMT-B: Trail Making Test-Part B; UPDRS-III: The Unified Parkinson's Disease Rating Scale-III (Motor section); VAN: Ventral attention network; VN: Visual network.

many of the studies mentioned above, revealed that the PD-MCI (n=222) group had decreased DMN connectivity compared to both the HC (n=353) and the PD-CN (n=289) groups and suggested that quantifying the connectivity of DMN as a biomarker for PD-associated cognitive impairment would be necessary for understanding the pathophysiology of the disease (42).

In the studies summarized, ICNs have been defined based on the characteristic of the BOLD signal. However, it is possible to perform studies on connectivity networks using different methods apart from analyzing the BOLD signal. Arslan et al. (2020), with the arterial spin labelling (ASL) method, which allows the measurement of cerebral blood flow, showed that there was hypoperfusion in the precuneus component of DMN in the PD-MCI group compared to the HC group. In addition, they classified the PD-MCI group in terms of H1/H1 and H1/H2 haplotypes associated with the MAPT gene polymorphism. They found that the H1/H1 haplotype of the PD-MCI group showed hypoperfusion in regions including the precuneus and anterior cerebellum components of DMN (43). Also, in an FDG-PET study, which allows the measurement of metabolic activity in the brain, it was found that the expression scores of the DMN component, including the precuneus, cingulum, and thalamus, were decreased in PD-MCI compared to PD-CN, and the expression scores of the ventral DMN are positively correlated with verbal recall scores (44).

The general conclusion that can be drawn from studies conducted on the continuum of PD-associated cognitive impairment is that DMN connectivity decreases as the severity of cognitive impairment increases. On the other hand, in two different studies conducted on the PD-associated cognitive impairment continuum, findings of increased DMN connectivity were also reported. In the first of these, it was found that the midline and frontal/temporal components of the DMN increased functional connectivity of the posterior DAN and FPN components in the PD-MCI group compared to both the PD-CN and HC groups, and this hyperconnectivity was found to be negatively related to the visuospatial function scores (45). A recent FDG-PET study showed increased metabolic DMN connectivity in the PD-CN and PD-MCI groups compared to the HC group, and both increased and decreased intra-DMN connectivity in various regions in the PD groups with and without cognitive impairment (46). In the same study, as a result of the analysis of DMN by ICA, it was found that DMN connectivity was decreased in PD-CN compared to HC but increased in PD-MCI compared to both HC and PD-CN. Besides, general cognition, visuospatial and attention scores were negatively

correlated with intra-DMN connectivity and positively correlated with executive functions scores.

Frontoparietal Network

The frontoparietal network (FPN) consists of bilateral dorsolateral prefrontal cortex and posterior parietal cortex components, which are associated with higher-level cognitive functions such as actively holding and processing information in working memory, problem-solving based on rules, and making decisions in the context of goal-directed behaviour (47). After DMN, FPN has been the most investigated ICN in the PD-associated continuum of cognitive impairment. Studies seem to agree that Parkinson's patients without cognitive impairment reveal lower FPN connectivity than HCs (33, 42, 48-50). In functional connectivity studies comparing PD-MCI and HC groups, findings were also reported that FPN connectivity was lower than that in HCs (36, 39, 42). However, a study investigating cerebral blood flow demonstrated hypoperfusion in areas involving FPN in PD-CN and PD-MCI compared to HC (43). In another study examining the relationship between brain-network topology and cognition in Parkinson's disease, it was found that HC and PD-CN groups were significantly more resistant to network disruption in FPN than in the PD-MCI group (50).

There are contradictory findings in studies comparing Parkinson's patients with and without cognitive impairment in terms of FPN. While Amboni et al. (2015) suggested that the FPN connectivity of the PD-MCI group was lower than that of the PD-CN group and that this low connectivity was positively associated with visuospatial functions, memory and attention scores (33), Baggio et al. (2015) suggested that the connectivity between FPN and DMN increased and increased connectivity was positively correlated with visuospatial scores (45). On the other hand, Pereza et al. (2017) reported decreased FPN connectivity in PD-MCI compared to PD-CN (48), and in parallel, Azamat et al. (2021) in Parkinson's disease dementia, reported hypoperfusion in regions involving FPN compared to PD-CN, PD-MCI, and non-demented Parkinson's patients by way of merging the two groups (51).

Dorsal and Ventral Attention Networks

Corbetta and Shulmann (2002) depicted two anatomically and functionally different attention systems in the human brain; the dorsal attention network (DAN) and the ventral attention network (VAN) (52). While DAN and VAN are considered two anatomically separated cortical systems with functionally specialized nodes that support specific processes for controlling attention, it has been shown that DAN includes the intraparietal sulcus and the frontal eye field, whereas VAN consists of the temporoparietal junction and ventral inferior frontal gyrus (IFG-pars orbitalis) components (53). While DAN is related to top-down processes in the goal-directed voluntary control of visuospatial attention, VAN plays a role in detecting unexpected bottom-up stimuli and triggering attention shifts (54). In initial studies performed (34, 45, 48), it was found that the connectivity of both within-DAN and DAN to other networks was lower in those with PD-MCI compared to both the PD-CN and HC groups, and this decreased connectivity was positively associated with executive function scores (45). It was also suggested that VAN connectivity was decreased in PD-MCI compared to PD-CN; however, there was no connectivity change in VAN in the comparison of HC and PD-CN (34, 48). In line with this finding, Arslan et al. (2020) revealed hypoperfusion in the regions involving DAN compared to HC in PD-MCI, and there was no change in DAN or VAN perfusion in the comparison of PD-MCI and PD-CN groups (43). A recent study comparing HCs with the PD-aMCI and PD-naMCI groups showed that DAN connectivity in the PD-MCI groups decreased compared to the HC group; however, there was no difference between the two PD-MCI groups (39). In addition, a PD-associated cognitive impairment continuum meta-analysis highlighted the importance of altered connectivity about cognition in PD, particularly in DAN and FPN (55).

Salience Network

The salience network (SN) emerges as an ICN containing cortical nodes covering the anterior cingulate cortex and ventral anterior insular cortices and subcortical components consisting of the amygdala, hypothalamus, ventral striatum, and the specific brainstem nuclei (56). One of the least explored networks in the PD-associated cognitive impairment continuum, SN is associated with responsiveness to homeostatically relevant stimuli and whether their valence is negative (punitive) or positive (reinforcing) (57). Findings related to SN were reported in only two of the studies covered in this systematic review. In the first of these studies (58), regions of interest of SN, DMN, and FPN were selected within the framework of a seed-based approach, and it was found that the intra-SN network coherence was higher in PD-CN compared to PD-MCI. However, they also suggested that SN-DMN connectivity was increased in the PD-MCI group compared to the PD-CN group. In addition, analyses based on graph theory displayed that the node degree of the SN and the scores of global cognition and visuospatial functions were positively correlated with the Trail Making Test Form B (TMT-B) score. In the second study, amnestic and non-amnestic PD-MCI groups were compared with the seed-based analysis method and revealed that the SN connectivity of the amnestic PD-MCI group was higher than both the non-amnestic PD-MCI and HC groups (39). In the same study, the patients were followed for 1-4 years, and it was reported that the risk of conversion to PD-associated dementia (PD-D) in patients with amnestic-type cognitive impairment was 2.3 times higher than in patients with PD without amnestic-type. In summary, it can be stated that as the severity of cognitive impairment increases in PD, the SN connectivity increases, but further studies are required.

Somatomotor Network

The foundation for the ICN studies was laid when Biswal et al. (1995) published the first study revealing that the bilateral motor cortices are not quiet at rest and that there is a high correlation between the BOLD time series of these regions suggesting ongoing information processing and functional connectivity (59). Within this framework, the somatomotor network (SMN) was the first ICN to be discovered. All of the studies covered in this systematic review have a common finding: SMN connectivity decreases in the continuum of PD-associated cognitive impairment. While Gorges et al. (2015) showed that patients with PD-MCI had decreased SMN connectivity compared to both PD-CN and HC (34), Pereza et al. (2017) showed that patients with PD-CN had decreased SMN connectivity compared to HC (37), Hou et al. (2021) revealed a decrease in connectivity in SMN compared to HC in newly diagnosed and drug-naive patients with PD-MCI. In addition, Hou et al. (2021) showed that SMN connectivity in a group of all Parkinson's patients was negatively correlated with UPDRS-III (Unified Parkinson's Disease Rating Scale – Motor Evaluation) scores (37). In parallel with functional connectivity studies, Arslan et al. (2020) reported SMN hypoperfusion in patients with PD-MCI according to both PD-CN and HC groups (43). Two studies on graph theory determined that patients with PD-MCI exhibited lower nodal centrality in SMN compared to patients with PD-CN (40) and HCs (41).

Visual Network

Studies on defining large-scale intrinsic connectivity networks revealed that the visual network (VN) consisted of two different components: the medial visual network (primary visual network) and the lateral visual network (extrastriate visual network). Anatomically, the medial visual network includes the primary visual cortices in the bilateral calcarine fissure (BA17), lingual gyrus, lateral geniculate nuclei, inferior precuneus, and the lateral visual network includes the visual association cortices (BA18, 19, and 37) (5). A longitudinal study of the PD-associated cognitive impairment continuum revealed that patients with PD-CN had decreased VN-FPN connectivity compared to patients with PD-MCI but increased VN-FPN connectivity in all Parkinson's patients after a one-

year of follow-up (49). However, in various studies, it has been found that patients with PD-CN and patients with PD-MCI show lower VN connectivity compared to healthy controls (36, 37, 48), and there is an expected positive correlation between VN connectivity and visuospatial functions scores (37). In two studies for the detection of cerebral blood flow, hypoperfusion was detected in the VN-containing regions in the PD-MCI group compared to HCs (43), and in the VN regions in the PD-D group compared to both the PD-MCI and PD-CN groups (51). Two studies with the graph theory approach revealed increased node centrality between VN nodes in PD-MCI compared to PD-CN (40) and HC (41). Based on these findings, it can be argued that as the severity of cognitive impairment increases in PD, there is a decrease in functional connectivity and perfusion of the VN regions, whereas the increase in the node centrality of the VN.

Auditory Network

The auditory network (AN) is a sensory network covering the primary (BA41 and 42) and secondary auditory cortices (BA22), including the Heschl gyrus, planum polare, planum temporale, lateral superior temporal gyrus, and posterior insular cortex (5). Findings related to AN were found in only two of the articles reviewed within the scope of this study. The first one showed that connectivity between AN and SMN decreased in patients with PD-MCI compared to HCs (36), and the other, the second study, which was a meta-analysis, indicated a decrease in AN connectivity in patients with PD-MCI compared to HCs (42).

DISCUSSION

This systematic review inspected twenty studies on ICNs in the Parkinson's disease-associated cognitive impairment continuum. In this framework, the focus is on the studies based on the default mode network (DMN), frontoparietal network (FPN), dorsal and ventral attention networks (DAN and VAN), salience network (SN), somatomotor network (SMN), visual network (VN) and auditory network (AN), which are frequently studied in the fMRI literature. It is possible to classify these connectivity networks as cognitive (DMN, FPN, DAN, VAN, SN) and sensory-motor networks (SMN, VN, AN) (7). It can be said that the results related to sensory-motor networks in the studies investigated within the scope of this review have internal consistency. The general opinion to draw from these studies is that the connectivity of SMN, VN, and AN decreases in the PD-associated cognitive impairment continuum. Nevertheless, consistent and inconsistent findings have been reported in studies on cognitive networks. Therefore, some points should be considered when interpreting the results from studies reviewed.

First, the criteria used in the diagnosis of PD-MCI may differ. Although the research conducted in line with the established criteria accepted by the Movement Disorders Society for diagnosing PD-MCI is reviewed within the scope of this study, there are two variations of MDS criteria, Stage I and Stage II, as mentioned in the introduction. Stage II criteria include a comprehensive neuropsychological assessment, while Stage I criteria can be considered an abbreviated assessment. In a study that compared these two criteria, Parkinson's patients without dementia were evaluated according to Stage I criteria with two different screening tests (Montreal Cognitive Assessment Scale, MoCA, and Parkinson's Disease-Cognitive Rating Scale, PD-CRS) and Stage II with a detailed neuropsychological evaluation, and the obtained groups were examined in terms of structural (voxel-based morphometry and cortical thickness), and functional (functional connectivity and graph theory) changes. In these assessments, Stage II criteria were set as the gold standard (60). In groups diagnosed with PD-MCI by PD-CRS and in the one diagnosed with PD-MCI according to Stage II criteria, a decrease in grey matter concentration was detected in the precuneus and posterior cingulate cortex, which are structures belonging to DMN, as well as a reduction of cortical thickness in the precuneus. However, no overlapping results were obtained in groups diagnosed according to Stage II criteria and MoCA. Nonetheless, in the seed-based analysis of ICNs, no functional connectivity difference was observed between PD-CN and PD-MCI in groups diagnosed with PD-MCI according to Stage II criteria and MoCA, but in the group diagnosed with PD-CRS, connectivity within the SN was found to be higher in the PD-CN group than in the PD-MCI group. However, it was reported that connectivity between DMN-SN and DMN-FPN was higher in the PD-MCI group compared to PD-CN. As a result of the analyses carried out within the framework of graph theory, it was found that the node degree of a node in two nodes of the SN and the centrality of a node of the DMN were higher than PD-MCI in PD-CN in all three diagnostic groups. The node degree of one node in the SN was higher in the PD-MCI group than in the PD-CN group in groups diagnosed with MoCA according to Stage II. On the other hand, it was reported that the centrality of a different node in the SN was higher than PD-MCI in PD-CN according to the diagnosis with MoCA, while it was higher than PD-CN in PD-MCI according to the Stage II diagnosis (60). There were also outcomes in only one PD-CRS, MoCA, and Stage II diagnostic group. PD-MCI is a risk factor for PD-D (61, 62); studies have shown that both Stage I and Stage II diagnostic criteria have prognostic validity for PD-D development. However, the sensitivity and specificity of Stage I criteria are considered lower than Stage II (19).

Another issue is the fluctuations between PD-MCI and PD-CN in the PD-associated cognitive impairment continuum. In longitudinal studies, it has been determined that approximately 20-30% of patients with a diagnosis of PD-MCI revert to normal cognition (63 - 66). However, it has also been reported that patients who revert to normal cognition can return to the MCI stage and that the risk of dementia increases in the long term (60, 65). A meta-analysis study showed that the rate of return to normal cognition in PD-MCI according to Stage I criteria is approximately two times higher than in patients diagnosed according to Stage II criteria (67). In a study carried out in Türkiye, it was determined that 20.8% of patients diagnosed with PD-MCI revert to normal cognition within an average of 1.5 years of follow-up, and education was an important variable in reverting to normal cognition. In addition, a decrease in grey matter concentration was found in the regions including FPN and VAN in patients with stable PD-MCI compared to patients reverting to normal cognition (68). However, no study based on ICNs included the PD group reverting to normal cognition in the PD-associated cognitive impairment continuum. In this context, longitudinal studies are required to understand better the relationships between cognitive profile fluctuations and large-scale connectivity networks. However, benign PD-MCI, which rarely progresses to dementia and is associated with frontostriatal dopaminergic deficiency, and malign PD-MCI, a serious risk factor for dementia and associated with posterior cortical deficits, have not been investigated based on ICNs. In particular, a longitudinal investigation of FPN connectivity in benign PD-MCI and VN connectivity in malign PD-MCI is required.

One reason for the inconsistencies between the results presented on cognitive connectivity networks in the studies reviewed in this systematic review may be that the PD groups in all studies consisted of patients under treatment except in three studies (35, 37, 41). It is known that newly diagnosed Parkinson's patients also meet the diagnosis of PD-MCI at rates varying between 20% and 55% (69-71). Since dopaminergic therapy used in Parkinson's disease affects cognition and ICNs (72-76), comparing newly diagnosed and drug-naive PD-MCI and PD-CN patients may be of significant importance in elucidating the neural basis of cognitive impairment in PD.

It was observed that none of the twenty studies reviewed had a PD group with subjective cognitive impairment, and only two included PD-D. A longitudinal study revealed that approximately 30% of Parkinson's patients with subjective cognitive complaints developed cognitive impairment

within two years (77). In this context, patients with subjective cognitive complaints should also be included in longitudinal neuroimaging studies, and the relationships between connectivity networks and the risk of developing cognitive impairment should be clarified. Wolters et al. (2019) included patients from the PD-D group in their meta-analysis. However, they combined the PD-MCI and PD-D groups in statistical analyses to obtain a PD group with a single cognitive impairment (42). In this context, there are restricted results about alterations in large-scale connectivity networks in Parkinson's disease-associated dementia. Long-term follow-up of Parkinson's patients on a continuum from subjective cognitive impairment to dementia may help identify various risk factors for the development of both mild cognitive impairment and dementia.

CONCLUSION

Throughout the Parkinson's disease-associated cognitive impairment continuum, there seems to be varying degrees of alterations in ICNs. It can be stated that these changes manifest themselves as a decrease in connectivity in sensory-motor networks. It is considered that well-controlled longitudinal studies are required to reveal the changes in cognitive networks. In future studies, it is crucial to define the cognitive disorder groups well and control the changes in connectivity networks due to dopaminergic treatment. Conducting longitudinal studies, especially in patients with subjective cognitive impairments and extending to dementia with extended follow-up periods may reveal the pathophysiological mechanisms underlying PD-associated cognitive impairment and may benefit the use of ICNs as a biomarker.

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