



Review Article

Application of Functional MRI in Parkinson's Disease and Default Mode Network: Review of the Literature

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ABSTRACT: Parkinson's disease (PD) has become the second most prominent neurodegenerative disorder relating to aging individuals. PD involves the loss of neurons containing dopamine in the midbrain and leads to a number of motor issues as well as non-motor complications such as cognitive and psychological abnormalities. The default mode network (DMN) is a complex brain network primarily active during rest and serves multiple roles relating to memory, self-referential processing, social cognition and consciousness and awareness. Multiple brain regions are involved in the DMN such as the medial prefrontal cortex (mPFC), the posterior cingulate cortex (PCC), the inferior parietal lobule, the precuneus and the lateral temporal cortex. Normal DMN connectivity is vital to preserving consciousness and self-awareness. Neurological pathologies such as PD disrupt DMN connectivity, leading to complex issues. Functional MRI (fMRI) is a neuroimaging modality used to observe brain activity through measuring blood flow differences as it relates to brain activity. DMN connectivity experiments using fMRI find that individuals with PD exhibit impaired DMN connectivity in specific regions including the PCC, mPFC and the precuneus. Individuals with greater PD motor symptoms have also been found to suffer larger alterations in DMN connections anatomically within the frontal lobe and PCC. While fMRI has been utilized as a tool to explore the relationship between PD patients and DMN connectivity, future research should look to develop a better understanding of the specific mechanisms of action that drive this link between DMN abnormality and PD severity.

RÉSUMÉ : Application de l'imagerie par résonance magnétique fonctionnelle à la maladie de Parkinson et au réseau du mode par défaut : une revue de la littérature. La maladie de Parkinson (MP) est devenue le deuxième trouble neuro-dégénératif [GB1] le plus important chez les personnes vieillissantes. La MP sous-tend la perte de neurones contenant de la dopamine dans le mésencéphale et entraîne un certain nombre de problèmes moteurs ainsi que des complications non motrices telles que des anomalies cognitives et psychologiques. Le réseau du mode par défaut (RMD) est un réseau cérébral complexe, principalement actif au repos, qui joue de multiples rôles dans la mémoire, le traitement autoréférentiel, la cognition sociale, la conscience et l'éveil. De nombreux composants cérébraux sont par ailleurs impliqués dans le RMD, tels que le cortex préfrontal médian (CPFM), le cortex cingulaire postérieur (CCP), le lobule pariétal inférieur (LPI), le précuneus et le cortex temporal latéral (CTL). La connectivité normale du RMD est essentielle à la préservation de la conscience et de la conscience de soi. Les pathologies neurologiques telles que la MP perturbent la connectivité du RMD, ce qui entraîne des problèmes complexes. L'imagerie par résonance magnétique fonctionnelle (IRMf) est un dispositif de neuro-imagerie utilisé pour observer l'activité cérébrale en mesurant les différences de flux sanguin en relation avec l'activité cérébrale. Les expériences sur la connectivité du RMD réalisées à l'aide de l'IRMf montrent que les personnes atteintes de la MP donnent à voir une altération de la connectivité du RMD dans des régions spécifiques, notamment le CCP, le CPFM et le précuneus. On a également constaté que les personnes présentant les symptômes moteurs les plus marqués de la MP souffraient d'altérations plus importantes des connexions du RMD au niveau anatomique dans le lobe frontal et le CCP. Bien que l'IRMf ait été utilisée comme outil pour explorer la relation entre les patients atteints de la MP et la connectivité du RMD, des recherches futures devraient viser à mieux comprendre les mécanismes d'action spécifiques à l'origine du lien entre les anomalies du RMD et la gravité de la MP.

Keywords: default mode network; functional MRI; Parkinson's disease; connectivity; review

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Background

Parkinson's disease (PD) is a neurodegenerative pathology that affects 3% of individuals by the age of 65 and rises to 5% for those over 85 years of age.¹ PD is characterized by the decrease of

dopaminergic neurons in the substantia nigra pars compacta of the midbrain, as well as increases of alpha-synuclein positive cytoplasmic inclusions, referred to as Lewy bodies, in the remaining neurons.² The physiological degeneration of the dopaminergic neurons in the substantia nigra pars compacta

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contributes to various motor pathologies,³ including resting tremors, rigidity, bradykinesia and gait problems.⁴ Furthermore, non-motor symptoms of PD involve cognitive deviations; psychiatric issues including apathy, anxiety and depression; sleep disorders including REM behavior disorder and insomnia; and autonomic dysfunctions.⁴

The default mode network (DMN) is an extensive brain system primarily activated during periods of rest, specifically when the brain is not primarily active in goal-directed activity.⁵ The DMN plays multiple roles related to memory, self-referential processing, social cognition and consciousness and awareness.⁵ The brain regions involved in the DMN include the medial prefrontal cortex (mPFC), the posterior cingulate cortex (PCC), the inferior parietal lobule (IPL), the precuneus and the lateral temporal cortex.⁶ The PCC and precuneus play a key role in the DMN's involvement in autobiographical memory retrieval.⁷ The mPFC plays a key role in the DMN's self-referential processing role, which is involved in reflection and evaluation of one's past experiences, current emotions and self-thinking.⁸ The IPL and mPFC are also involved in the DMN's role in social cognition, which involves the "theory of the minds," a process where individuals are aware and understanding of other people's intentions and perspectives.⁹ Furthermore, DMN regulates human awareness and consciousness.⁵ Studies suggest disruptions in DMN connectivity alter consciousness, and decreased DMN connections lead to decreased human awareness.¹⁰ These findings further suggest the importance of DMN for preserving a strong self-awareness and understanding of reality.¹¹

Studies suggest that various neurological pathologies have led to abnormalities in DMN connectivity.¹² Many past articles have discussed the impact of PD on DMN activity using functional MRI (fMRI). This review aims to evaluate how fMRI has been used to assess alterations in DMN connectivity for individuals with PD, with particular focus on the relationship between DMN dysfunction and cognitive and motor symptom severity. We further note methodological limitations of current fMRI approaches and highlight key directions for future research.

Methodology

The following literature review was conducted to present current research findings using fMRI to study the effects of PD on the DMN. We included studies investigating the role of PD on DMN (until August 2024) in PubMed and EMBASE (including Medline). The keywords searched for this study include Default Mode Network, Parkinson's Disease and Functional Magnetic Resonance Imaging. References obtained from studies included within the review were also incorporated. Emphasis was placed on only reviewing literature that utilized fMRI to conduct DMN testing for individuals with PD. Excluded studies include those not in English, as well as those utilizing alternative methods to measure DMN activity.

Results

Default mode network and Parkinson's disease

The later-stage non-motor PD symptoms involving neuropsychiatric issues and cognitive problems are heavily linked to connectivity issues within the DMN.¹³ This decreased connectivity is associated with multiple cognitive issues for individuals with PD such as poorer executive functioning, worsening memory and

diminished success in daily functions requiring memory.¹⁴ Overall, these issues contribute to worsened cognitive functioning.¹⁵ Moreover, studies show that there is a negative link between the severity of PD motor symptoms and the level of connectivity in the DMN.¹⁶ Individuals with greater PD motor symptoms have also been found to suffer larger alterations in DMN connections.¹⁶ Findings such as these propose a link between the DMN and multiple symptoms of PD including both cognitive and motor issues.¹⁵

Studying default mode network and Parkinson's disease using fMRI

Resting-state fMRI has been utilized to measure DMN activity and observe impaired DMN connectivity in individuals with PD.²⁴ Current studies utilizing fMRI technology have found that individuals with PD exhibit impaired DMN connectivity in specific regions, including the PCC, mPFC and the precuneus.²⁵ Individuals with greater PD motor symptoms have also been found to suffer larger alterations in DMN connections anatomically within the frontal lobe and PCC.²⁶ An overview of studies assessing alterations in DMN connectivity using fMRI for PD patients is included in Table 1.

It is notable that throughout the reviewed studies, participant treatment conditions, whether treatment-naïve, actively partaking in levodopa or dopaminergic therapy, were not consistently reported. Dopaminergic medications enhance neural drive, which may influence DMN connectivity.³⁶ Therefore, it is possible that there is some variability across the included results, an important factor to consider when interpreting the overall findings.

Discussion

Observing the relationship between PD progression and DMN connectivity using fMRI

Mechanisms underlying DMN disruption in PD

Several hypotheses have been proposed attempting to explain DMN connectivity changes for individuals with PD.³⁸ Although current research cannot identify the direct mechanism by which PD affects DMN connectivity, multiple hypotheses have been derived based on existing research. One such hypothesis suggests that the decrease in dopaminergic neurons in the brain for individuals with PD results in altered DMN connectivity.¹⁷ Other theories highlight the potential roles of other neurotransmitters, such as serotonin and cholinergic systems, which are also affected by PD and may influence DMN connections.¹⁸

Another potential hypothesis for DMN connectivity issues proposes that the loss of dopaminergic neurons' functioning and abundance as well as the observed neurochemical brain changes in PD patients contributed to the abnormal DMN connectivity found in individuals with PD.³⁸ Researchers suggest that when dopaminergic neurons are lost, a cascade of dopamine depletion is caused in PD patients in the striatum, leading to altered DMN connectivity.³⁸ Furthermore, the involvement of other neurotransmitter systems including the serotonergic and cholinergic systems has also been found to be linked to DMN connectivity issues for PD patients.¹⁸

An additional theory for DMN connectivity issues proposes alterations in biochemical pathways and concentrations as a possible explanation.³⁹ Researchers propose that neuroinflammation and mitochondrial dysfunction may have roles and serve as contributing factors that lead to DMN connectivity disruption for individuals with PD.⁴⁰ Furthermore, scientists also propose the

Table 1. Observing alterations in DMN connectivity using fMRI for PD patients

Author	Sample size	Participant age range	Methodology	Disease stage	Study modality	Study objective	Main findings
Tessitore A, et al., 2012 ²⁵	16 cognitively unimpaired patients with PD and 16 age and gender-matched healthy controls	N/A	Seed-based analysis utilizing the PCC to assess DMN connectivity in PD patients vs controls	Cognitively unimpaired patients with PD	Observational study	Investigate the functional integrity of the DMN for people with PD who do not exhibit cognitive impairments	Decrease in DMN connectivity linked to motor symptom severity
Chen L, Huang T, Ma D, Chen YC., 2022 ²⁶	50 healthy controls and 50 individuals with PD	62.88 ± 9.06 years old	Seed-based analysis utilizing PCC as a seed to monitor DMN connectivity. Preprocessed through band-pass filtering, smoothing and motion correction	Individuals with PD scoring 27.76 ± 11.79 on the UPDRS-III scale and 1.41 ± 0.45 on the Hoehn and Yahr scale	Observational study	Investigated if changes in DMN functional connectivity are correlated with cognitive decline for PD patients	PD patients displayed stronger brain connections in regions such as the PCC and right angular gyrus, which is correlated with motor symptom severity.
Lucas-Jiménez O, Ojeda N, Peña J, Díez-Cirarda M, Cabrera-Zubizarreta A, Gómez-Esteban JC, Gómez-Beldarrain MÁ, Ibarretxe-Bilbao N., 2016 ¹⁴	37 PD patients and 16 healthy controls	45–75 years old	Utilized seed-to-voxel analysis on six DMN regions (PCC, ACC, MTL, IPC, MPFC, precuneus) utilizing the CONN toolbox. Preprocessed through CompCor denoising, band-pass filtering and normalization	Hoehn and Yahr PD disease stage 1, 2 or 3	Observational study	Assess whether functional neural connectivity is disrupted between regions of the DMN for people with PD	Observed decreased FC between PCC and MTL regions, leading to decreased cognitive performance and increased gray matter loss in PCC, medial temporal and parietal brain regions, as well as white matter loss affecting visual and memory abilities.
Putcha D, Ross RS, Cronin-Golomb A, Janes AC, Stern CE., 2016 ²⁷	24 individuals with PD, 20 age/education matched controls	62.5 ± 6.4 years old for individuals with PD and 65.9 ± 9.4 years old for controls	Resting-state fMRI utilized through independent component analysis (ICA) to identify the DMN, salience network (SN) and the central executive network. Functional network connectivity monitored DMN-SN coupling. Preprocessing involved motion correction, temporal filtering and normalization	UPDRS total score of 27.1 ± 10.8, UPDRS motor score of 16.1 ± 7.2, Hoehn and Yahr stage 1–3	Observational study	Investigate if the relationship between the DMN and SN relates to cognitive performance for both PD patients and healthy older controls	Observed that PD patients displayed strong cognition when there was a strong balance between salience and DMN activity while PD patients with disrupted balance displayed cognitive decline.
Ruppert MC, Greuel A, Freigang J, et al. (2021) ¹⁵	60 PD patients and 25 healthy controls	65.02 ± 9.82 years old for PD patients and 63.52 ± 7.67 years old for healthy controls	Used ICA on resting-state fMRI and [18F]-fluorodeoxyglucose positron emission tomography data to find the DMN	UPDRS-III total of 24.67 ± 9.13 H and Y stage 1, 2 or 3	Observational study	Investigate the correlation between intrinsic metabolic and functional connectivity issues within the DMN and their relevance for cognitive symptoms in PD	Observed decreased DMN connection for PD patients with MCI in areas of the brain related to problem-solving, hypothesizing that network reorganization may occur as metabolism worsens

(Continued)

Table 1. Observing alterations in DMN connectivity using fMRI for PD patients (*Continued*)

Author	Sample size	Participant age range	Methodology	Disease stage	Study modality	Study objective	Main findings
Bejr-kasem H, Pagonabarraga J, Martínez-Horta S, et al. (2018) ²⁸	18 patients with PD and minor hallucinations and 14 patients with PD and no minor hallucinations	>54 years old	Utilized seed-to-voxel connectivity with a 100 mm spheric seed centered in the PCC. Also utilized exploratory seeds in the mPFC and bilateral parahippocampal cortex. Preprocessing involved realignment, slice-timing correlation and smoothing	N/A	Observational study	Explore functional and structural changes characterized by minor PD hallucinations, specifically in visual-processing areas.	Found PD patients who had minor VH exhibited changes in DMN areas that were similar to major VH patients, proposing that minor VH can be used to predict major VH for PD patients.
Yao N, Shek-Kwan Chang R, Cheung C, Pang S, Lau KK, Suckling J, Rowe JB, Yu K, Ka-Fung Mak H, Chua SE, Ho SL, McAlonan GM. (2014) ²⁹	14 healthy controls (HC), 12 individuals with PD but without VH, 12 individuals with PD and VH	HC age range 64.1 ± 4.0 years old PD non-VH 63.4 ± 7.4 years old PD and VH 67.6 ± 7.4 years old	Utilized ICA to identify the DMN and assess connectivity differences between groups. Preprocessing involved smoothing, motion correction and spatial normalization	For PD non-VH 2.8 ± 0.9 Hoehn and Yahr disease stage and 18.0 ± 12.9 UPDRS-III score For PD and VH 3.2 ± 0.7 Hoehn and Yahr stage and 20.9 ± 10.6 UPDRS-III score	Observational study	Investigate DMN alterations correlating with VH for people with PD	Found that individuals with PD who had minor VH displayed decreased DMN activity compared to healthy controls but greater connectivity compared to PD patients without VH, proposing that sensory processing in VH can be influenced by DMN issues.
Franciotti, R., Delli Pizzi, S., Perfetti, B., Tartaro, A., Bonanni, L., Thomas, A., Weis, L., Biundo, R., Antonini, A., & Onofri, M. (2015) ³⁰	15 healthy controls, 15 multiple system atrophy patients, 15 early PD patients, 30 severe PD patients (15 with and 15 without VH)	>= 55 years of age	ICA utilized to measure DMN activity and connection between groups. Standard preprocessing steps included spatial normalization and motion correction	Early and severe PD patients	Observational study	Analyze changes in DMN connection and activity in PD patients without VH, multiple system atrophy patients and healthy controls	Individuals with PD and minor VH displayed different DMN connectivity than PD patients without minor VH and healthy controls
Ooi LQR, Wen MC, Ng SY, Chia NS, Chew IHM, Lee W, Xu Z, Hartono S, Tan EK, Chan LL, Tan LC. (2019) ³¹	81 PD patients without excessive daytime sleepiness (EDS) and 17 PD patients with EDS	PD without EDS group had an average age of 62.77 years old and PD EDS group had an average age of 65.35 years old	Utilized ICA to isolate the posterior DMN and compared DMN connectivity strength between early-stage PD patients with and without EDS. Preprocessing involved spatial normalization to MNI space, spatial smoothing and motion correction	PD without EDS group had a UPDRS-III average score of 19.75 and PD EDS group had a UPDRS-III average score of 21.94	Observational study	Investigate the relationship between increase posterior DMN activity and EDS for early-stage PD patients	Found PD patients who had EDS also had more posterior DMN activity, proposing that having EDS may be correlated with attention deficits and compensatory brain mechanisms

Table 1. Observing alterations in DMN connectivity using fMRI for PD patients (*Continued*)

Author	Sample size	Participant age range	Methodology	Disease stage	Study modality	Study objective	Main findings
Franciotti R, Delli Pizzi S, Russo M, Carrarini C, Carrozzino D, Perfetti B, Onofri M, Bonanni L. (2019) ³²	22 controls, 18 individuals with PD, 18 individuals with PD and somatic symptoms disorder (SSD)	Controls age range 63 ± 9 years old, PD age range 64 ± 8 years old, PD patients with SSD 66 ± 7 years old	Seed-based functional connectivity approach targeting the DMN and SN. Functional connectivity and fractional amplitude of low-frequency fluctuations were computed. Preprocessing involved temporal band-pass filtering, normalization and motion correction	PD patients had a score of 14 ± 5 on the UPDRS-III scale and 1.5 ± 0.5 on the Hoehn and Yahr scale. PD patients who also had SSD had a score of 16 ± 7 on the UPDRS-III scale and 1.6 ± 0.4 on the Hoehn and Yahr scale	Study the relationship between somatic symptom disorder for PD patients and DMN and SN abnormalities		Suggest a link between DMN dysfunction and somatic symptom disorder (SSD) in PD, due to decreased DMN and SN connectivity for SSD PD patients compared to PD patients without SSD and healthy controls.
Junli Li, Changlian Tan, Lin Zhang, Sainan Cai, Qin Shen, Qinru Liu, Min Wang, ChenDie Song, Fan Zhou, Jiaying Yuan, Yujing Liu, Bowen Lan, Haiyan Liao. (2023) ³³	95 PD patients and 37 healthy controls	>= 55 years of age	Multivariate pattern analysis was used to decode motion attributes between visual and social-cognitive regions. Preprocessing involved smoothing, motion correction and spatial normalization to MNI space	50 early/mid-stage PD patients, 45 early/moderate-stage PD patients	Observational study	Investigate how human brain encodes complex biological motion attributes through neural mechanisms	Found that early- and moderate-stage PD patients displayed decreased DMN activity during executive control, showing that as PD worsens, brain network disruptions become more widespread
Schindlbeck KA, Vo A, Mattis PJ, Villringer K, Marzinzik F, Fiebach JB, Eidelberg D. (2021) ³⁴	Three cohorts: Cohort A had 153 PD patients, Cohort B had 23 PD and 15 healthy controls, Cohort C had 22 PD and 19 healthy controls	Cohort A age between 51 and 79 years old, Cohort B age between 61 and 81 years old, Cohort C age between 50 and 67 years old	ICA utilized to analyze ventral and dorsal DMN subdivisions. Preprocessing involved realignment, smoothing with a Gaussian kernel and normalization	Cohort A UPDRS-III score between 9 and 43, Cohort B UPDRS-III score between 20 and 44, Cohort C UPDRS-III score between 14 and 34	Observational study	Examine changes in DMN subdivisions for PD patients while analyzing their relationship to cognition	Cognitive problems in PD are correlated with a pattern known as PD cognition-related pattern, which overlaps with DMN, as less DMN activity was found to correlated with cognitive decline
Hou, Y., Yuan, X., Wei, Q. <i>et al.</i> (2020) ³⁵	28 drug-naïve PD patients with mild cognitive impairment (MCI), 19 drug-naïve PD patients with cognitively unimpaired and 28 age- and sex-matched healthy controls	>50 years of age	Utilized functional connectivity strength metrics focusing on DMN subtypes. Preprocessing involved smoothing, spatial normalization, slice-timing correction and motion correction. The analysis was voxel-wise with cluster correction	Mild to moderate PD stages	Observational study	Investigated DMN subtype disruption for drug-naïve PD patients with MCI while exploring the potential as a biomarker for cognitively impaired PD patients	Found that PD patients with MCI exhibited decreased DMN activity, specifically in the medial prefrontal cortex, which can be used to differentiate individuals from cognitively healthy PD patients.
Zhong, J., Guan, X., Zhong, X., Cao, F., Gu, Q., Guo, T., Zhou, C., Zeng, Q., Wang, J., Gao, T., & Zhang, M. (2019) ³⁶	24 non-demented PD patients before and after taking levodopa and 36 healthy controls	>= 52 years of age	Utilized seed-based connectivity employing the PCC as the seed to assess DMN connectivity. Preprocessing involved slice timing, motion correction, spatial smoothing and normalization to MNI space	Mild to moderate PD stages	Experimental study	Investigated the effect of levodopa on DMN connections in non-demented PD patients to find if dopaminergic therapy can restore DMN connections to healthy control levels	Found levodopa treatment increased DMN connectivity for PD patients, proposing dopamine therapy may restore DMN connectivity

(Continued)

Table 1. Observing alterations in DMN connectivity using fMRI for PD patients (Continued)

Author	Sample size	Participant age range	Methodology	Disease stage	Study modality	Study objective	Main findings
Sang L, et al. (2015) ³⁷	26 right-handed PD patients without dementia, 30 healthy controls	PD patients aged 54.31 ± 10.90 years old, Controls aged 56.81 ± 10.81 years old	Utilized a graph theory approach derived from 90 ROIs in the AAL atlas. Connectivity between all ROI pairs was calculated to construct whole-brain networks. Network topology was assessed through degree centrality, clustering coefficient, modularity and global and local efficiency. Preprocessing involved slice-timing correction, motion correction, spatial smoothing and normalization to MNI space	PD patients UPDRS motor score off medication of 18.96 ± 8.86 and Hoehn and Yahr score off medication of 1.26 ± 0.45	Observational study	Investigated alterations in the topological organization of large-scale functional brain networks in early-stage PD patients receiving antiparkinson treatment. Monitoring changes in hub distribution, modular structure and global efficiency	Observed PD patients had reduced overall DMN connectivity but maintained connectivity in smaller areas of the brain. Found that hub region and network structure changes affected cognitive and motor areas.

FC = functional connectivity; IPC = inferior parietal cortex; MTL = medial temporal lobe; PCC = posterior cingulate cortex; PD = Parkinson's disease; VH = visual hallucinations; RIO = regions of interest; ACC = anterior cingulate cortex.

possibility that the uncharacteristic spread of alpha-synuclein pathology, which is a known symptom of PD patients, may also play a role in disrupting the normal connectivity of the DMN for individuals with PD.³⁹

DMN connectivity and disease progression

Despite these potential hypotheses, researchers have noticed a relationship between PD progression and DMN connectivity using fMRI measurement techniques.¹⁶ Research shows that a decrease in DMN connectivity was linked to worsening PD motor symptoms by severity.¹⁶ These cross-sectional study findings propose that PD has a large and varying effect on different brain networks, related to both motor and non-motor PD symptoms.²⁶

Aside from these cross-sectional PD and DMN interventions, examinations utilizing longitudinal methods and fMRI have been conducted to better learn the mechanisms through which DMN connectivity is altered as PD conditions progress for individuals.¹⁶ Interventions illustrate that as individuals with PD experience their condition worsen over time, DMN connections also progressively decrease among these individuals, specifically for PD patients who develop cognitive problems.²⁶ These findings suggest that continuous DMN alteration and loss of connectivity over time may be a key contributor to worsening motor symptoms and cognitive symptoms for individuals with PD.²⁶

Conflicting results regarding DMN connectivity in PD have been reported across studies. Tessitore and colleagues found diminished DMN connectivity in patients with PD, with lower connectivity correlating with an increase in motor symptom severity.²⁵ Conversely, Chen et al. observed an increase in connectivity among certain DMN regions, specifically the PCC and the right angular gyrus, both of which are centers associated with motor symptom severity. These inconsistencies may reflect differences in study methodologies, such as variations in disease stage, medication statuses, seed placement strategies and data preprocessing approaches.²⁶ These inconsistencies suggest that DMN connectivity alterations among patients with PD are likely region-specific, rather than reflecting a uniform pattern across the network, highlighting the influence of disease heterogeneity. Standardization of imaging protocols and clinical characterization across future investigations are essential to resolve these divergences.

Therapeutic modulation of DMN connectivity

Therapeutic interventions utilizing resting-state fMRI have been implemented to study the effects of clinical dopaminergic interventions on the connectivity of the DMN for individuals with PD.⁴¹ A previous meta-analysis of fMRI examinations found that dopaminergic therapy was able to partially restore DMN connections, specifically in the regions of the mPFC and the PCC.⁴¹ These findings suggest that dopamine replacement therapy could be implemented to modify DMN connectivity for individuals with PD by improving DMN connections to normal levels, possibly resulting in an improvement in both cognitive and motor symptoms for PD patients.⁴¹

Variability across PD phenotypes

fMRI studies have also noticed that different subtypes of PD have exhibited varying effects on DMN connectivity.⁴² Studies examining different PD phenotypes show that alterations in DMN connectivity are not uniform across all subtypes.⁴² For

instance, patients with the tremor-dominant subtype displayed abnormal connectivity patterns primarily within the posterior DMN regions, while patients with the postural instability and gait difficulty (PIGD) subtype exhibited further disruptions in frontal DMN regions.⁴² These findings suggest that motor phenotype influences the spatial pattern of DMN dysfunction, potentially reflecting differing underlying pathophysiology between tremor-dominant and PIGD phenotypes. This information proposes the idea that changes in DMN connectivity may be related and vary due to the different clinical PD phenotype an individual carries.⁴² These fMRI findings hint at PD being a heterogeneous and complex pathology, with varying effects on DMN and connectivity depending on different subtypes of the disease.⁴²

Limitations

Employing resting-state fMRI as a measurement tool presents some limitations in practice. One issue presented by fMRI technology is the low temporal resolution provided as compared to other counterparts.²⁰ Due to fMRI measuring the hemodynamic response time needed for changes in blood flow based on neural stimulation, fMRI temporal resolution takes place in seconds, rather than milliseconds.²⁰ fMRI results may also be negatively altered due to participant head movements or physiological noise, which can promote faulty data if not corrected during analysis.⁴³ Another prominent issue is inter-tester variability when it comes to recording the BOLD signal. Although the BOLD signal is indicative of blood flow change, neural activity is not directly measured, making it difficult to differentiate between the mix of vascular and neural factors reflected in the signal.²⁰

Future directions

Although much research has been conducted related to PD and DMN, many drawbacks remain, which can be aimed to improve for the future. One problem is the lack of depth of understanding regarding the specific mechanisms through which PD alters DMN connectivity. While fMRI studies propose a correlation between the severity of PD and DMN connectivity, the exact physiological process and mechanism through which this occurs remains unknown. Future investigations should explore the specific mechanism of action through which decreased dopamine levels, neurotransmitter abnormalities, alpha-synuclein changes and neuroinflammation cause altered DMN connectivity for PD patients.

Furthermore, another concern is the lack of studies investigating the effect of PD on DMN connectivity related to neuropsychiatric PD symptoms as opposed to cognitive and motor symptoms. While some studies have been done exploring neuropsychiatric symptoms such as depression and their effect on DMN connectivity, many more studies have investigated the relationship between DMN abnormalities and motor and cognitive PD symptom severity. Future research should be conducted exploring other neuropsychiatric PD symptoms such as sleep disorders and hallucinations, to learn how and if these symptoms also relate to DMN abnormalities for PD patients. Moreover, while some research has been conducted exploring the different impact of differing PD subtypes on DMN connectivity, more research needs to be done to learn how each specific PD subtype differently affects DMN connectivity and if specialized clinical solutions can be tailored to cater to these different subtypes and improve DMN connectivity for PD patients.

The lack of longitudinal studies is also an issue. While most current studies are cross-sectional and provide an understanding of DMN connectivity at a specific time-point, further examinations should monitor longitudinal studies to observe changes in DMN connectivity over a long period of time as PD severity increases and cognitive and motor symptoms worsen.

Another weakness is the lack of research pertaining to utilizing DMN connectivity as a biomarker for disease progression. While literature proposes using fMRI to monitor DMN connectivity as a biomarker for PD severity progression and success of treatment interventions, further research is needed to create standard protocols to permit observing DMN connectivity as a biomarker for treatment interventions.

As DMN results have shown promise as a potential biomarker for disease progression, professionals should explore how these insights can be applied in clinical patient care rather than remaining restricted to research-based initiatives.

Conclusion

PD is a complex pathology exhibiting a myriad of motor, cognitive, neuropsychiatric and other symptoms. The DMN is an important brain network involved in resting-state functions as well as in brain tasks related to memory and executive functioning. fMRI has been used as a tool to understand the relationship between abnormal DMN connectivity and PD and the various symptoms correlated with the pathology. While current research implies a relationship between PD progression and motor and cognitive symptom severity and DMN dysfunction, future interventions should explore the concrete mechanisms of action leading to these problems, through the utilization of fMRI as an imaging tool to reach a more comprehensive understanding of the correlation between DMN dysfunction and PD progression for individuals with PD.

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