

Systematic Review on the resting state fMRI in Parkinson's disease and cognitive impairment

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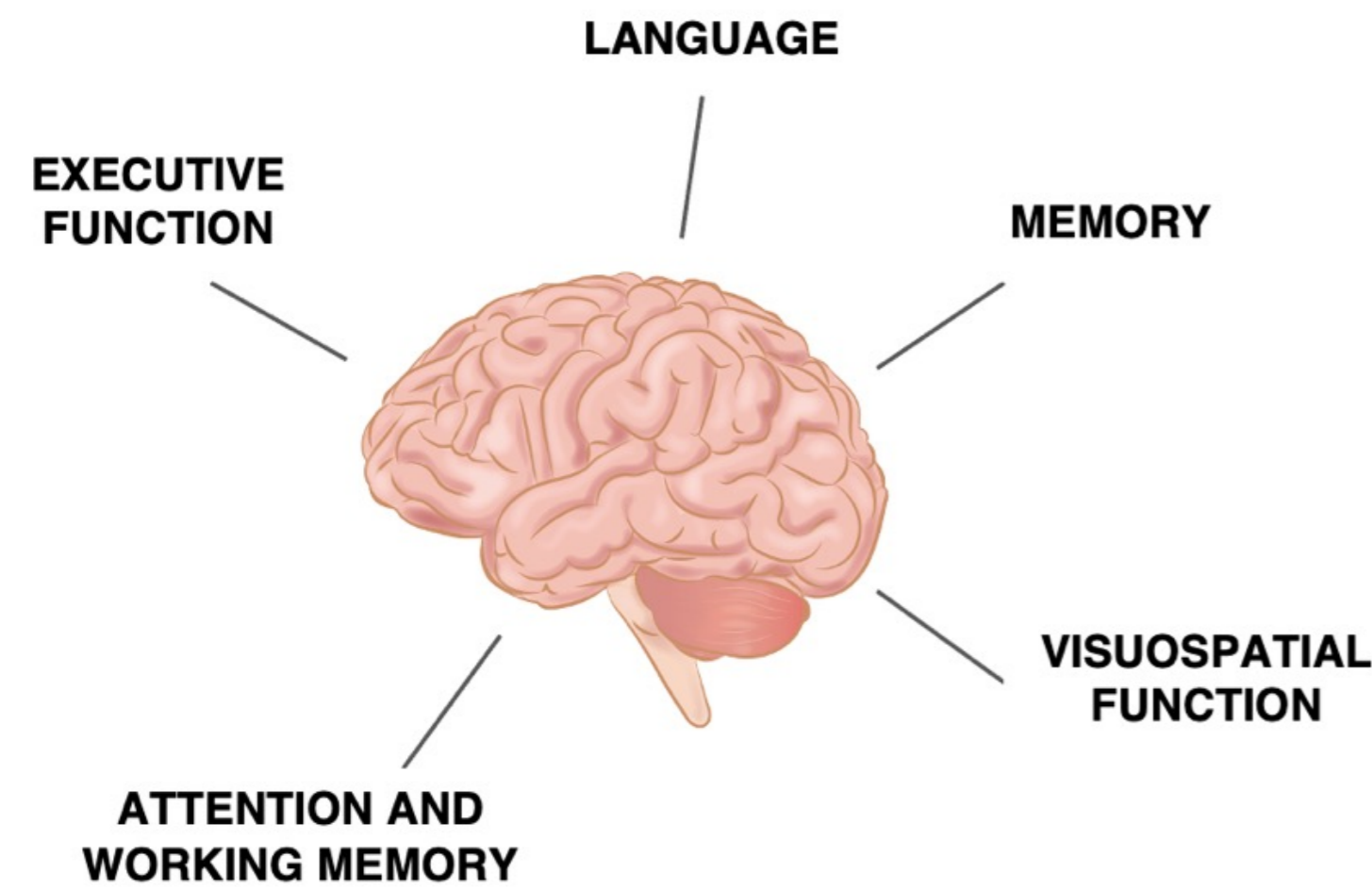
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INTRODUCTION

Cognitive impairment is now recognised as an important non-motor symptom in Parkinson's disease (PD). Despite its detrimental impact on patients' quality of life and contribution to a high disease burden, the underlying neural mechanism of cognitive impairment and its subtypes in PD has yet been fully elucidated.

The clinical profile for cognitive impairment in PD is heterogeneous and can affect cognitive domains.



A systematic review is conducted to identify altered functional connectivity between brain regions and networks during resting state fMRI (rs-fMRI) contributing to various cognitive subtypes in PD.

METHODS

- **4 databases** PubMed, Scopus, Embase and PsycINFO were searched.
- **Search terms used:** (Parkinson*) AND ('resting state' OR rest*) AND (fMRI OR 'functional magnetic resonance imaging') AND ('global cognit*' OR memory OR visuospatial OR executive* OR attention OR 'working memory' OR cognit* OR dementia).
- **Studies were only included if they:** 1) were written in English, 2) involved idiopathic PD patients, 3) performed fMRI during resting state and 4) used cognitive measures.
- For this preliminary study, only studies exploring PD-mild cognitive impairment (PD-MCI) were included

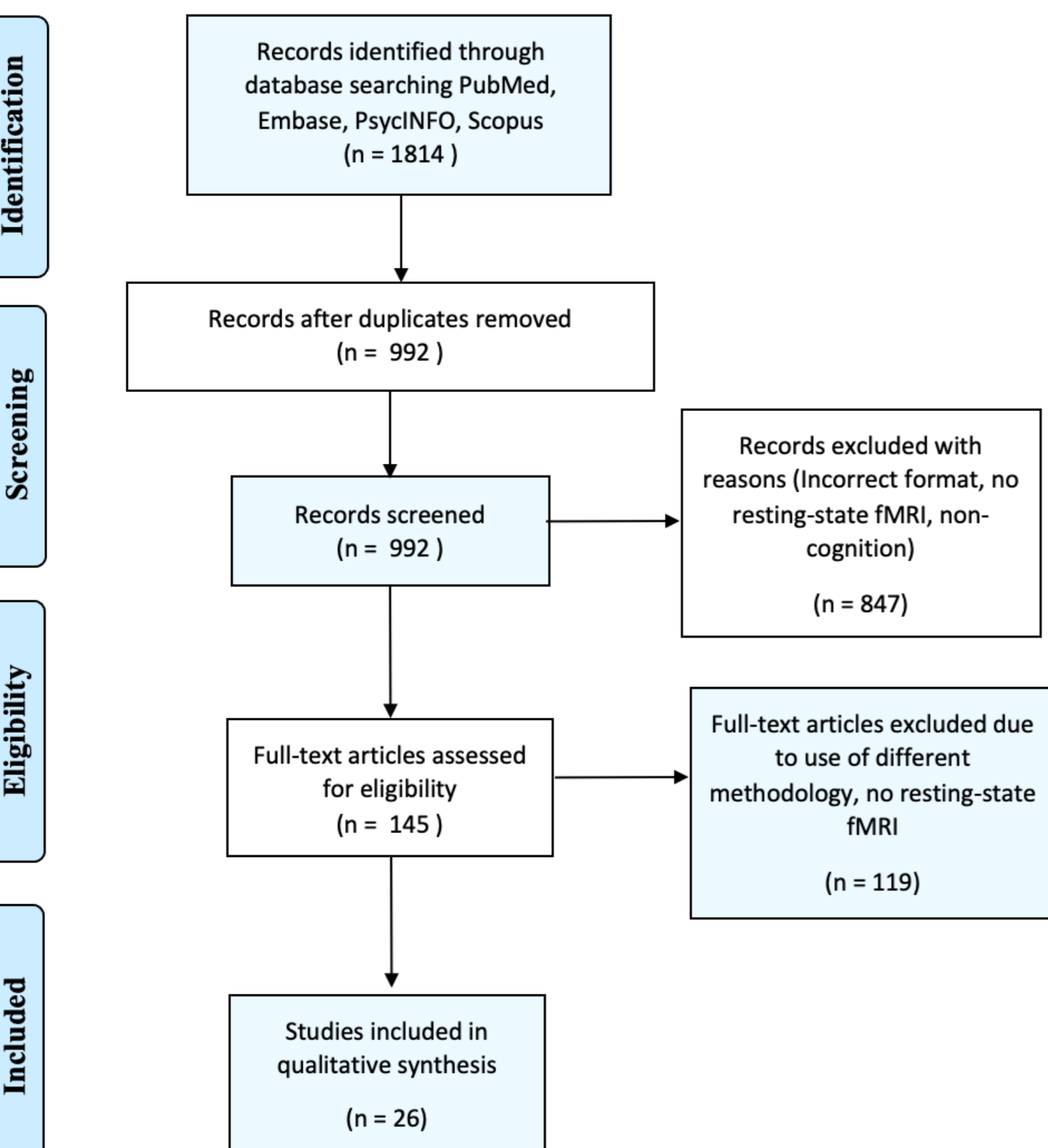


Figure 1: PRISMA Flow Diagram

References

1. Litvan I, Goldman JG, Troster AI, Schmand BA, Weintraub D, Petersen RC, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. *Mov Disord.* 2012;27(3):349-56.

RESULTS

Database searches 1814 records (Fig 1). A total of 145 records were read in full text from which 119 were excluded. 26 articles included in this preliminary review.

Movement Disorder Society (MDS)'s Level I and II criteria are currently used to diagnose PD-MCI amongst researchers and clinicians.(1)

- Mini-Mental State Examination (MMSE) and/or Montreal Cognitive Assessment (MoCA) was used to assess global cognition
- Various neuropsychological tests used to assess the 5 cognitive domains

Studies were divided according to the different analytical method used and study-specific information, Levodopa equivalent daily dose (LEDD), MDS Level and main study findings were recorded (Table 1, 2, 3, 4).

SEED/ROI ANALYSIS

AUTHOR, YEAR	SUBJECT	LEDD	MDS LEVEL	MAIN FINDING
Abos, 2017	43 PD-NC, 27 PD-MCI, 38 HC	ON	2	Connectivity in frontal or anterior cingulate regions and associated with memory and executive function.
Bezdrcek, 2019	18 PD-NC, 16 PD MCI, 31 HC	ON	2	FC of the anterior hippocampus and precuneus/superior parietal cortex associated with memory and visuospatial domain. L. hippocampus and superior parietal cortex correlated with language.
Chen, 2017	11 PD-NC, 21 PD MCI, 21 HC	ON	2	In PD-NC and PD-MCI, FC of PCC of the right ITG and bilateral Pcu was correlated with global cognition, while PCC of bilateral Pcu, R. middle Ocg, and angular gyrus was associated with global cognition.
Chiang, 2018	16 PD-NC, 13 PD MCI, 12 PDD	OFF	2	Worse global cognition, attention, and memory with reduced FC between MOL and MTL. Increased pons FC was associated with higher global cognition and greater impairment in attention and memory.
Engels, 2018	24 PD, 27 HC	OFF	1	dFC of DMN associated with visuospatial function but not with executive function and memory function.
Gargouri, 2019	52 PD, 25 HC	ON	1	Connectivity in medial septal nucleus and nucleus of the vertical limb of the diagonal band correlated with memory, whereas olfactory bulb and amygdala correlated with global cognition and executive functions.
Hou, 2016	18 PD-NC, 14 PD-MCI, 22 HC	OFF	2	Decreased FC between ATL and MTG correlated with attention/working memory and reduced FC between hippocampal formation and IFG correlated with memory.
Jia, 2019	27 PD-NC, 27 PD-MCI, 25 HCl	ON	2	Precuneus FC strength in right striatum was positively associated with memory performance.
Palmer, 2020	62 PD, 33 HC	OFF	1	Lower FC of cSMN to bilateral precentral gyrus, post-central gyrus, SMA and R. SPL and higher FC between cDAN with R. postcentral gyrus and precentral gyrus with higher global cognition.
Pan, 2022	13 PD-NC, 25 PD-MCI, 17 HC	OFF	2	FC between L. dAI and R. SPG negatively correlated with memory and executive function. Difference in FC between R. dAI and R. DCG correlated with attention/working memory, visuospatial function and language.
Wang, 2021	13 PD-NC, 20 PD-MCI, 13 HC	ON	1	Decreased FC within bilateral precuneus impacted episodic memory in PD-MCI
Zhan, 2018	9 PD-NC, 9 PD-MCI, 9 PDD, 9 HC	ON	2	Positive correlation between global cognition and strength of PCC connectivity in angular gyrus and posterior cerebellum.
Baggio, 2015	43 PD-NC, 22 PD-MCI, 36 HC	ON	2	PD-MCI had positive correlation between Cth in the left lateral occipital/temporo-occipital cluster and visuospatial scores.
Li, 2021	25 PD-NC, 25 PD-MCI, 25 HC	ON	1	Altered degree centrality in left FFG and left precuneus were correlated with global cognition in PD-MCI

Table 1: 14 Seed-based or region of interest (ROI)-based studies

ICA ANALYSIS

AUTHOR, YEAR	SUBJECT	LEDD	MDS LEVEL	MAIN FINDING
Peraza, 2017	62 PD-NC, 37 PD-MCI, 30 HC	ON	2	Disconnection between frontal pole network and right middle frontal gyrus affected working memory. Decreased dorsal-medial pre-frontal network clusters in pre-and postcentral gyri was associated with executive function and planning.
Wang, 2018	19 PD-NC, 10 PD-MCI, 13 HC	OFF	1	Activity in opercular part of right inferior frontal inferior lobe was negatively correlated with global cognition, attention, executive functioning and working memory, compared to PD-NC
Amboni, 2015	21 PD-NC, 21 PD-MCI, 20 HC	ON	1	Positive correlation between visuospatial scores and FC of left PFC and right PFC. Positive correlation between memory, executive function/attention and left PFC FC. No significant correlation with cognition and DMN FC.

Table 2: 3 Independent component analysis studies

GRAPH THEORY ANALYSIS

AUTHOR, YEAR	SUBJECT	LEDD	MDS LEVEL	MAIN FINDING
Baggio, 2014	43 PD-NC, 23 PD-MCI, 36 HC	ON	2	Measures of clustering, degree and BC had negative correlation with visuospatial in temporal and parietal cortices, basal ganglia, thalamus and medial temporal nodes. Memory scores correlated with frontal and temporal areas and negatively in prefrontal and occipital areas.
Nagano-Saito, 2019	20 PD-NC, 15 PD-MCI, 21 HC	ON	2	Increased hub function in precuneus and cingulate cortex were positively correlated with all cognitive domains.
Suo, 2023	17 PD-NC, 24 PD-MCI, 24 HC	OFF	2	Positive correlation between global cognition and intramodular connectivity of DMN module (II) and cerebellum module (VI), and intermodular connectivity between DMN module (ii) and frontal-parietal module (II) than PD-NC.

Table 3: 3 Graph theory-based studies

ReHO/fALFF ANALYSIS

AUTHOR, YEAR	SUBJECT	LEDD	MDS LEVEL	MAIN FINDING
Li, 2020	36 PD-NC, 33 PD-MCI, 22 HC	ON	1	Negative correlation between global cognition and FC of bilateral MCC/left PCC. Positive correlation between global cognition and FC of left SOG/MOG/left cuneus/left precuneus.
Kang, 2016	21 PD-NC, 18 PD-MCI, 22 HC	OFF	1	Increased ReHo values in prefrontal cortex including R. SFG, R. MFG and orbitofrontal cortex in PD-MCI but causality with cognitive impairment is unclear.
Li, 2020	25 PD-NC, 25 PD-MCI, 25 HC	ON	1	ReHo value of left precuneus was negatively correlated with global cognition whereas left insula was significantly positively correlated with MoCA score in PD. PD-MCI had increased spontaneous synchrony in left precuneus than PD-NC.
Guo, 2021	16 PD-NC, 20 PD-MCI, 20 HC	ON	1	ReHo value in the R. precuneus, L. triangular IFG, L. MFG, R. opercular IFG, L. orbital IFG, L. SMG, L. angular gyrus, L. ITG, and R. cerebellum 7b correlated positively with whereas ReHo value in the L. PCG and L. FG negatively correlated with global cognition.
Xing, 2021	19 PD, 30 PD MCI, 21 HC	ON	1	PD MCI had increased ReHo in the L. MOG, L. IPL and R. PCG compared to PD.
Rong, 2021	42 PD-NC, 24 PD-MCI, 33 HC	ON	2	FC of left middle temporal lobe was higher in PD-MCI than PD-NC and positively correlated with global cognition.

Table 4: 6 Regional Homogeneity (ReHo) and/or Fractional amplitude of low-frequency fluctuations (fALFF) based studies

CONCLUSION

Cognitive activities require the coordination of various brain regions and networks. This systematic review, to the best of our knowledge, is the first study exploring resting-state neural connectivity in Parkinson's disease patients with cognitive impairment according to the cognitive subtypes.

The review is currently in the analysing phase and we are sharing our search strategy, relevant background and preliminary results.

The findings of this study will potentially contribute to the identification of potential diagnostic markers and targeted treatments for each of cognitive domain impairment in PD.