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Review article

Resting-state fMRI in Parkinson's disease patients with cognitive impairment: A meta-analysis

Amée F. Wolters[a,*], Sjors C.F. van de Weijer[a], Albert F.G. Leentjens[b,c], Annelien A. Duits[c], Heidi I.L. Jacobs[d,e], Mark L. Kuijf[a]

[a] Department of Neurology, Maastricht University Medical Centre, P.O. Box 5800, 6202, AZ, Maastricht, the Netherlands
[b] Department of Psychiatry, Maastricht University Medical Centre, P.O. Box 5800, 6202, AZ, Maastricht, the Netherlands
[c] Department of Neuropsychology, Maastricht University Medical Centre, P.O. Box 5800, 6202, AZ, Maastricht, the Netherlands
[d] School for Mental Health and Neuroscience, Alzheimer Center Limburg, Maastricht University, P.O. Box 616, 6200, MD, Maastricht, the Netherlands
[e] Department of Radiology, Division of Nuclear Medicine and Molecular Imaging, Massachusetts General Hospital and Harvard Medical School, 55 Fruit Street, Boston, MA, 02114, USA

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ABSTRACT

Background: Cognitive impairment is a common non-motor symptom in Parkinson's disease. So far, the underlying pathophysiology remains unclear. Several alterations in functional network connectivity have been described in Parkinson's disease patients with cognitive impairment which are probably the result of the heterogenous pathophysiology underlying this cognitive decline, including dopaminergic and cholinergic deficits. Accordingly, the reported resting-state connectivity patterns vary greatly among studies.

Objective: To evaluate the localization and magnitude of functional connectivity patterns in resting-state brain networks in Parkinson's disease patients with cognitive impairment by pooling data from available studies.

Methods: We searched PubMed, the Cochrane Library, MEDLINE, Embase and PsycINFO to identify functional MRI studies in Parkinson's disease patients with cognitive impairment. A voxel-based meta-analysis combined with quality statistics was performed, using the anisotropic effect-size version of the signed differential mapping method.

Results: Seventeen studies with cognitively impaired Parkinson's disease patients were included consisting of 222 Parkinson's disease patients with mild cognitive impairment, 68 patients with Parkinson's disease dementia, 289 cognitively unimpaired Parkinson's disease patients and 353 healthy controls. Parkinson's disease patients with cognitive impairment predominantly showed a reduced connectivity in specific brain regions that are part of the default mode network.

Conclusion: Cognitive impairment in Parkinson's disease is associated with reduced connectivity in networks relevant to cognition, most prominently the default mode network. Specific alterations in functional connectivity may contribute to cognitive decline in Parkinson patients and may be a promising future biomarker.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease and is characterized by motor symptoms such as bradykinesia, rigidity and tremor [1–3]. Moreover, patients with PD also experience a broad spectrum of non-motor symptoms such as neuropsychiatric disturbances and autonomic dysfunction. Already in the earliest phases of the disease, cognitive impairment (CI) can be found in up to 42.5% of the PD patients [4]. Furthermore, up to 80% of the patients eventually develop Parkinson's Disease Dementia (PDD) in the advanced stages of the disease [5,6]. Patients with PD experiencing mild cognitive impairment (MCI) are at a higher risk of subsequently developing PDD [7].

The pathophysiological mechanism of cognitive impairment in Parkinson's disease patients has not yet been elucidated and no valid biomarkers have been identified [8]. Research in this field has focused on the formation of protein aggregates, neurotransmitter system dysfunction as well as genetic risk factors and underlying pathways. Lewy-

* Corresponding author. Department of Neurology, Maastricht University Medical Centre, P.O. Box 5800, 6202, AZ, Maastricht, the Netherlands.
E-mail addresses: amee.wolters@mumc.nl (A.F. Wolters), sjors.vande.weijer@mumc.nl (S.C.F. van de Weijer), a.leentjens@maastrichtuniversity.nl (A.F.G. Leentjens), aa.duits@mumc.nl (A.A. Duits), h.jacobs@maastrichtuniversity.nl (H.I.L. Jacobs), mark.kuijf@mumc.nl (M.L. Kuijf).

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body depositions, formed by neuronal alpha-synuclein aggregates, cause the loss of mesencephalic dopaminergic neurons and result in the typical dopaminergic deficit in the basal ganglia of PD with CI [9–12]. In addition, differences in cerebral levels of Aβ-amyloid depositions as shown in PET-studies suggest a differential role in cognitive deterioration and development of dementia in PD patients [13]. A previous study of Compta et al. (2011) suggested that it is the combination of cortical amyloid deposits and cortical Lewy bodies that has the most predictive value for the development of CI in PD [14]. The spatial distribution of neuronal dysfunction also plays a role in the "dual syndrome hypothesis" [15]. This suggests that (1) dopaminergic dysfunction in the fronto-striatal regions is more involved in a subgroup of PD patients with MCI and predominantly deficits in planning, working memory and executive functions, whereas (2) cholinergic dysfunction within the posterior cortical and temporal lobes is more involved in early deficits in visuo-spatial function and semantic fluency and a more rapid cognitive decline to dementia [15]. Indeed, several lines of research indicate that besides dopaminergic dysfunction the noradrenergic, serotonergic and cholinergic systems are also affected in PD patients. Dysfunctional neurotransmitter synaptic activity within the locus coeruleus [16–18], dorsal raphe nuclei [19,20], and cholinergic brainstem nuclei [21] respectively have all been associated with degeneration within these structures in PD. However, as suggested by the dopaminergic overdosing theory, dysfunction of the relatively less effected ventral cortico-striatal circuits, involved in reward processing and learning, may also arise due to an overdose of dopamine in these areas [15,22–25]. From another perspective, several genotypes, such as APOE ε4, MAPT, H1 haplotypes and GBA mutation [26–30] are increasingly recognized as potential risk factors for dementia in PD and may shed new light in pathophysiological mechanisms of PD-MCI [31–34]. This also points to the direction that there may be several mechanisms involved in CI and the development of dementia in PD [8].

Of interest, several neuroimaging techniques are able to characterize the pathological substrates of PD and other neurodegenerative disorders [35]. One promising method is resting-state functional MRI, which has shown the ability to explore the functional activity in different brain networks in a reliable and reproducible way [36,37]. It has been reported that alterations in several neurotransmitter systems influence the functional brain activity measured with fMRI [38–42]. Additionally, a correlation was reported between the loss of dopaminergic neurons and alterations in functional brain network activity in PD [43]. Since the basal ganglia are part of neuronal networks involving the entire cortex, one can expect that reductions in dopaminergic release will affect the functioning of many large-scale cerebral networks relevant for cognitive processing [44]. Furthermore, it has been suggested that an abnormal alpha-synuclein level in the cerebrospinal fluid influences both sensorimotor and non-motor functional connectivity networks in PD [45]. Based on these results, there has been growing interest in using functional magnetic resonance imaging (fMRI) to investigate the neural basis for CI in PD. By measuring intrinsic blood oxygen level-dependent (BOLD) low-frequency signal fluctuations, fMRI can be used to detect interregional correlations in specific brain networks during rest [46,47].

Various studies have investigated the resting-state networks in PD-MCI and PDD and disruptions are predominantly described in the default mode network and the fronto-parietal network [37,48–54]. The default mode network is thought to serve an important role in several higher order cognitive functions, such as autobiographical memory and imagining the future, while the fronto-parietal network is predominantly involved in attention and cognitive control [37,55]. Unfortunately, results between studies vary greatly and most fMRI studies consist of small samples.

In this study, we pool functional connectivity data in resting-state brain networks of PD patients with CI by means of a voxel-based meta-analysis. The aim of this study is to obtain a better understanding of the functional connectivity networks involved in PD with CI and to provide evidence as to whether fMRI results could serve as a biomarker for PD with CI. Based on previous studies, we hypothesize that PD patients with CI show reduced resting-state brain connectivity compared to healthy controls and PD patients without CI. We specifically expect to observe these alterations most prominently in the default mode network and fronto-parietal network.

2. Methods

2.1. Search strategies and study selection

A literature search in PubMed, Medline, Embase, PsycINFO and the Cochrane Library was performed. For this search, the following search terms were used: ((Parkinson's disease) OR (Parkinson)) AND ((Mild cognitive impairment) OR (MCI) OR (Parkinson's disease dementia) OR (Dementia) OR (Cognitive impairment)) AND ((fMRI) OR (functional MRI)). Afterwards, the reference lists of the included articles were searched for additional eligible publications. The final search was conducted on the 30th of April 2018 and resulted in a total of 1122 articles.

For this meta-analysis, we included resting-state fMRI studies comparing a group of cognitively impaired PD patients (PD-CI) with either a sample of healthy controls (HC) or a sample of PD patients without CI. Studies comparing the functional connectivity patterns of HC or PD with dementia with Lewy bodies were not included. Furthermore, only studies applying a whole-brain analysis, independent component analysis or seed-based analysis, with a correlation of the seeds to voxels encompassing the entire brain, were included in this meta-analysis. To prevent the results from being biased towards certain region of interest, studies performing a region of interest analysis were excluded. Other exclusion criteria were: 1. Undefined PD with CI study groups or not enough information provided to determine whether CI was present; 2. No resting-state fMRI; 3. Review articles reporting no original data; or 4. Conference proceedings without full report publication. Three manuscripts had to be excluded because they focused on global connectivity and network topological parameters and did not report specific changes on a regional or voxel-level [56–58].

First, duplicates were removed from the search results, followed by screening of the abstracts independently by two researchers (AW, SW). When any discrepancies existed between the included articles, this was resolved in a consensus meeting. When no consensus was reached, a third specialist was consulted (MK). The following information was extracted from each included study: first author, year of publication, published journal, sample size, MRI type, definition of CI, statistical analysis technique and patient characteristics (UPDRS score, age, dopaminergic medication, LEDD, and MMSE or MoCA-score). Peak coordinates and effect size measures of the regions with a significant difference in functional connectivity were also collected. Some publications did not report peak coordinates and therefore the relevant authors were contacted by e-mail to request this information.

2.2. Quality assessment

To our knowledge, there are no official guidelines for assessing the quality of fMRI studies. Therefore for the overall quality assessment of the reports in this meta-analysis, we derived our own criteria from the guidelines for reporting fMRI studies as described by Poldrack et al. (2009) [59]. This resulted in nine quality criteria, which comprise of the following domains: (1) Inclusion and exclusion procedure and patient demographics; (2) fMRI procedure and patient instructions; (3) Spatial normalization method; (4) Determination of the regions of interest; (5) Reproducibility of the analysis; (6) Statistical tests used to substantiate the results; (7) Correction for the multiple testing problem; (8) Figures and tables; (9) Quality control measures. Studies could score 0, 0.5 or 1 point for each item. An overall score of $\geq$7.5 was considered as good, 4–7.5 as fair and $\leq$4 as poor quality. See supplementary data

S1 for further specification of the criteria. Quality assessment was performed by two researchers (AW, SW) and discrepancies were discussed until consensus was reached. If no consensus could be reached, a third specialist was consulted (HJ).

2.3. Data analysis

This meta-analysis was carried out using the anisotropic effect size version of signed differential mapping (AES-SDM) [60,61]. This validated voxel-based meta-analyses approach has been used in meta-analysis of several other neuropsychiatric studies [62–67]. AES-SDM is specifically designed to combine neuroimaging studies with studies reporting solely peak coordinates in coordinate systems (e.g. MNI, Talairach). The peak coordinates and their statistical values are used to recreate a statistical parametric map for each study. This map is created by using the effect sizes of the differences between patients and controls. Subsequently, a random-effects variance-weighted image-based meta-analysis is conducted in each voxel. In this meta-analysis, we applied the default AES-SDM kernel size and thresholds (FWHM = 20 mm, voxel p = 0.005, peak height SDM-Z = 1, cluster extent = 10 voxels). The SDM-Z score represents a probability measure. In the random-effects analysis the results are thresholded to this given probability, to detect if more studies report functional connectivity changes near a certain voxel than would be expected by chance [61,62,68].

To assess the residual heterogeneity of the results, examination of the funnel plots of the peaks coordinates was carried out. This allowed us to check whether the results were driven by one or very few studies and to detect gross differences in study results. These funnel plots were statistically tested with Egger's regression test. To further assess the robustness of the results, we performed a jack-knife analysis within AES-SDM, in which the meta-analysis is systematically repeated as many times as studies have been included, subsequently removing one different study at a time.

After performing the statistical analysis, the spatial layout of these results was compared with the intrinsic connectivity network templates as described by Smith et al. (2009) [69]. These templates were obtained from the BrainMap database [70–72]. We performed a spatial correlation analysis in FSL to determine the degree of spatial overlap between our map with peak coordinate clusters and these well-defined functional networks. This also includes a calculation of the number of voxels of our peak coordinate clusters inside the resting-state network templates as a percentage of the total number of voxels in the clusters. Afterwards we visually inspected these images to identify which peak coordinates led to the corresponding spatial correlation value.

3. Results

3.1. Demographic data and quality assessment

Seventeen studies met the in- and exclusion criteria and were included in this meta-analysis [48,49,52,73–86]. Among these, fifteen studies compared PD-CI with healthy controls (HC) and nine studies compared PD-CI patients to PD patients who were cognitively unimpaired (PD-CU). Two studies, from Madhyastha et al. (2015) and Canu et al. (2015), reported results for the comparison of HC to a group of PD patients comprising of both CU patients and patients with MCI [48,76]. Both studies were included because, firstly, the sample size of PD contained more MCI than PD-CU patients and, secondly, the PD group as a whole scored considerably worse on the neuropsychological assessment compared to the control group. The complete in- and exclusion procedure is displayed in Fig. 1. Altogether, these studies included 932 participants of which 353 HC, 289 PD-CU, 222 PD-MCI and 68 patients with PDD. Basic demographics of the participants per group are summarized in Table 1. Baseline characteristics showed a higher mean age for PDD (71.5) and PD MCI (66.9) when compared to PD CU (63.6) and HC (64.5). Additionally, as expected the PD MCI and PDD groups showed worse results regarding the global cognition scores. Moreover, higher mean LEDD and UPDRS-III scores were found in the PD-MCI and PDD subgroup, indicating more advanced stages of the disease.

The fMRI characteristics and statistical details of the included studies are described in Table 2. Eight of the studies performed a seed-based analysis [49,52,78–80,83,85,86], six studies performed an independent component analysis [48,73,75,76,81,84] and the three remaining studies adopted different whole brain methodologies [74,77,82]. Atrophy correction was applied in only six studies [52,75,77,79,80,83]. Twelve studies did not enter the subjects gray matter volume maps as a voxel-wise regressor in the group comparison [48,49,73,74,76,78,81,82,84–86]. However, three of these twelve studies conducted a voxel-based morphometry analysis [73,76,86], which did not show a significant difference between HC and PD-CI. Another study of Bezdicek et al. (2018) has also performed a voxel-based morphometry which did not show significant differences between PD-MCI and PD-CU, but the analysis did express significant differences in brain atrophy between HC and PD-MCI for which the results were not corrected [82].

Based on our quality assessment, all included studies reached a score of either ‘Good’ or ‘Fair’. Three studies were classified as fair [49,83,85]. The main reasons for this were the lack of motion or atrophy correction, inadequate normalization methods, or the fact that the in- and exclusion criteria and patient instructions for the resting-state fMRI were not clearly reported. All other studies had a total score above 7 and were therefore considered as being of good quality. Further specification of the quality assessment can be found in the supplementary data S1.

3.2. Regional changes in resting-state connectivity

The meta-analysis showed reduced functional brain connectivity in several brain regions in patients with PD-CI as compared to HC. More specifically, our meta-analysis demonstrated a reduced connectivity in PD-CI in the right Rolandic operculum, left inferior parietal gyri, right angular gyrus, left parahippocampal gyrus, right calcarine fissure, right superior frontal gyrus and right precentral gyrus as compared to the HC (see Table 3, Fig. 2A). An increased functional connectivity in PD-CI was found in the right supramarginal gyrus when compared to the HC group.

For the contrast PD-CU vs. PD-CI, lower connectivity was detected in PD-CI patients in the left precuneus, right median cingulate gyrus, left superior frontal gyrus and right precentral gyrus. In addition, increased functional connectivity of the right cerebellum (hemispheric lobule VI) was found in the PD-CI group as compared to PD-CU (see Table 3, Fig. 2B).

3.3. Robustness analysis

The robustness analysis was performed with the Egger's linear regression method and visual inspection of the jack-knife analysis. See supplementary data S2 for further specification of the funnel plots and this analysis. The Egger's test showed a significant asymmetry regarding the funnel plot of the right Rolandic operculum, with a p-value smaller than 0.1. None of the other reported peak coordinates in this study showed an intercept that significantly differed from zero ($P > 0.1$). Visual inspection of the jack-knife analysis for the contrast of HC vs. PD-CI, exhibited a poor reproducibility of the peak coordinate in the right precentral gyrus (BA 6). With respect to the comparison of PD-CU with PD-CI patients, the right cerebellar region (BA 37) showed a somewhat lower reproducibility.

3.4. Network localization

We performed a spatial correlation analysis in which we compared

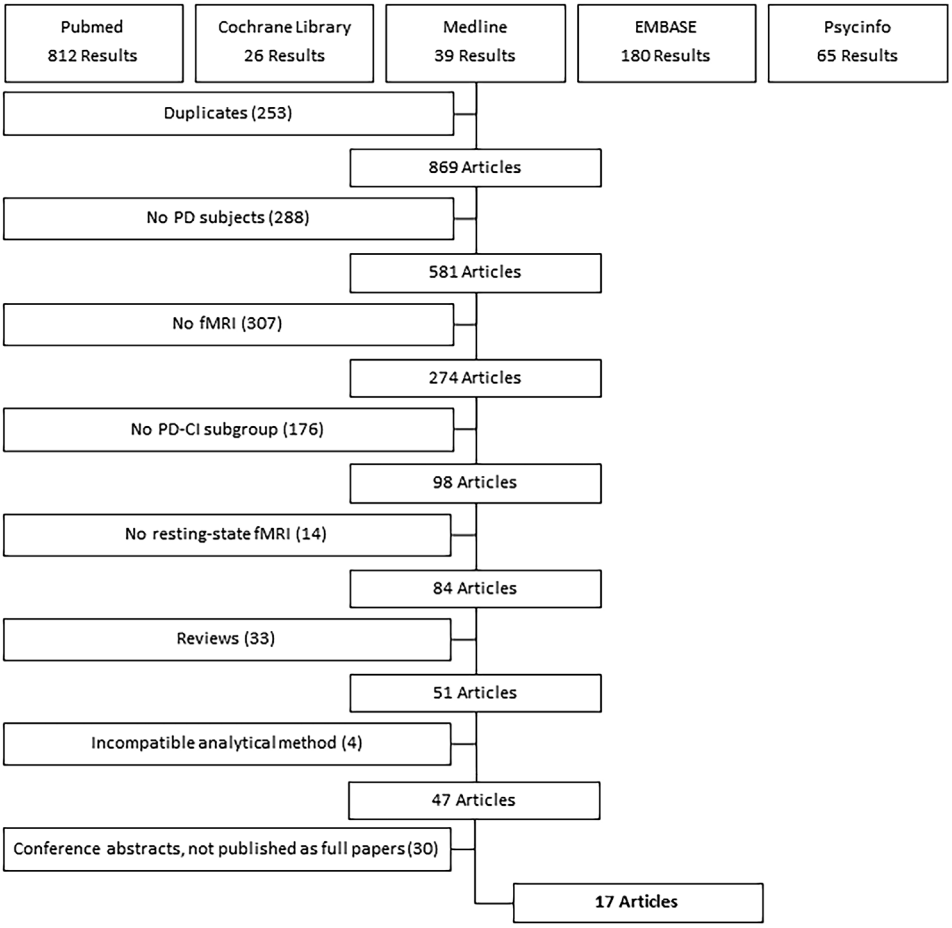

Fig. 1. Flowchart of the study selection procedure, performed according to the PRISMA 2009 guidelines.

the total brain map of our reported peak coordinates with the intrinsic connectivity network templates as described by Smith et al. (2009) to detect in which resting-state networks the peak coordinates are situated. With this analysis, a spatial correlation was found between our reported peak coordinates and several resting-state networks. For all associated networks, we have displayed both the spatial correlation coefficient (r) and the percentage of voxels of our peak coordinate clusters inside the resting-state networks as a fraction of the total number of voxels of our peak coordinate clusters. Regarding the contrast of HC vs. PD-CI, our analysis displayed a correlation between the total map of peak coordinates with a decreased connectivity in PD-CI and the auditory network (r = 0.13; 28,5%), the sensorimotor network (r = 0.13; 30,6%). Spatial correlation was also found to a lesser extent, in the right fronto-parietal network (r = 0.07; 14,4%) and default mode network (r = 0.07; 17,2%). Upon visual inspection, the spatial correlation with the auditory network appeared to be driven by the peak coordinate of the right Rolandic operculum and right precentral gyrus (BA 4). The observed spatial correlation with the sensorimotor network seemed to be based on the peak coordinate of the left inferior parietal gyri and precentral gyrus (BA 6). Moreover, predominantly the peak coordinate in the right Rolandic operculum explains the spatial correlation with the right fronto-parietal network. And finally, the peak coordinates of the right calcarine fissure and right angular gyrus were mainly associated with the default mode network. The peak coordinate in the right supramarginal gyrus, which showed an increased connectivity in PD-CI showed a correlation with the sensorimotor network (r = 0.05; 90,6%) and the right fronto-parietal network (r = 0.05; 36,1%).

For our second contrast, PD-CI vs PD-CU, we observed a decreased connectivity in PD-CI which correlated spatially specifically with the default mode network (r = 0.24; 66,2%). After visual inspection we noticed that the spatial correlation with the default mode network could be attributed to the peak coordinates in the left precuneus, right precentral gyrus and the right median cingulate gyrus. The peak coordinate in the right cerebellum, which displayed an increased functional connectivity for PD-CI as compared to PD-CU, did primarily show a notable spatial correlation with the cerebellar network (r = 0.19; 99,7%). For further specification of the spatial correlation analysis, see supplementary data S3.

4. Discussion

In this study, we aimed to evaluate the hypothesis that reduced functional connectivity changes in PD patients with CI can be detected in specific resting-state networks, as the disease induced dopaminergic deficits can have widespread repercussions on brain function. As expected, the found spatial correlation coefficients (r) with specific resting-state networks are rather low. The reason for this is that the results from our meta-analysis contain far fewer voxels than the large functional resting-state networks. The correlation analysis measures overlap and since our peak coordinates overlap only a small part of these networks, there are many voxels in the network not included. To provide more insight into the meaning of the spatial correlation results, we have therefore also provided the number of voxels of our peak coordinate clusters inside the network as a percentage of the total number of voxels of the clusters. Within our analysis, a reduced connectivity was found in the default mode network, auditory network and right fronto-parietal network when PD patients with CI were compared with HC. Furthermore, when comparing PD-CI with HC, we also noted a spatial correlation with the sensorimotor network, which could be

Table 1
Demographic characteristics of the included studies

Study	Sample Size				Age[1]				Medication ON/OFF	MMSE*/MoCA°				LEDD[1]			UPDRS-III[1]		
	HC	PD CU	PD MCI	PDD	HC	PD CU	PD MCI	PDD		HC	PD CU	PD MCI	PDD	PD CU	PD MCI	PDD	PD CU	PD MCI	PDD
Amboni et al. 2015 [73]	20	21	21	-	61.9 ± 9.2	65.8 ± 6.5	65.2 ± 8.7	-	ON	28.7 ± 0.9*	28.7 ± 1.4*	26.7 ± 1.8*	-	530.9 ± 299.4	453.1 ± 307.4	-	13.1 ± 5.3	14.3 ± 8.5	-
Baggio et al.2015 [75]	36	43	22	-	63.4 ± 10.5	64.0 ± 9.8	66.1 ± 12.2	-	ON	29.7 ± 0.5*	29.4 ± 0.9*	28.5 ± 1.2*		646.7 ± 419.2	951.9 ± 498.2		14.1 ± 7.5	18.2 ± 8.7	-
Bezdicek et al.2018 [82]	30	15	16	-	63.6 ± 8.1	64.8 ± 7.9	64.7 ± 7.9	-	ON	27.0 ± 2.2°	26.4 ± 1.9°	25.3 ± 2.6°	-	1447.2 ± 768.4	1305.8 ± 561.1	-	13.3 ± 6.4	15.1 ± 8.2	-
Borroni et al. 2015 [77]	10	11	-	10	62.2 ± 8.0	66.3 ± 3.8	-	74.5 ± 4.6	ON	NR (≥28*)	27.8 ± 1.8*	-	18.8 ± 3.4*	504.5 ± 336.4	-	714.2 ± 348.1	10.7 ± 5.4	-	27.9 ± 10.5
Canu et al.2015 [76]	35	10	13	-	67.7 ± 7.6	66.9 ± 8.0		-	UPDRS ON fMRI OFF	29.1 ± 1.0*	27.7 ± 1.8*		-	937.0 ± 435.9		-	25.4 ± 9.2		-
Chen et al.2015 [78]	21	19	-	11	61.1 ± 8.3	59.5 ± 8.8	-	64.1 ± 11.4	OFF	28.2 ± 1.2°	25.8 ± 2.8°	-	20.9 ± 1.6°	NR	-	NR	14.7 ± 6.3	-	18.6 ± 5.2
Chen et al.2017 [83]	21	11	21	-	61.1 ± 8.3	59.2 ± 5.1	63.6 ± 11.2	-	NR	28.3 ± 1.1°	27.1 ± 2.2°	22.6 ± 2.3°	-	NR	NR	-	16.0 ± 7.1	16.9 ± 5.4	-
Díez-Cirarda et al.2018 [84]	26	12	23	-	68.3 ± 7.5	65.2 ± 8.3	69.2 ± 4.5	-	ON	28.9 ± 1.3*	28.7 ± 1.3*	26.9 ± 2.1*	-	548.9 ± 459.6	904.52 ± 518.5	-	18.5 ± 6.9	22.7 ± 11.1	-
Gorges et al.2015 [52]	22	14	11	6	68 (65-73)	70 (65-77)	72 (64-74)		ON	30 (30-30)*	29 (28-30)*	27 (26-28)*		475 (205-880)	360 (231-620)		10 (5-13)	12 (9-18)	
Hou et al.2016 [80]	22	18	14	-	52.6 ± 6.7	53.6 ± 8.7	54.9 ± 8.1	-	OFF	NR	27.6 ± 2.2°	22.4 ± 2.6°	-	0	0	-	15.4 ± 5.6	17.8 ± 8.5	-
Madhyastha et al. 2015 [48]	21	11	13	-	61.9 ± 10.00	66.1 ± 10.3		-	ON	27.3 ± 2.0°	26.4 ± 2.2°		-	NR		-	23.1 ± 8.61		-
Peraza et al.2015 [79]	17	-	-	12	76.9 ± 5.8	-	-	71.5 ± 4.8	ON	29.1 ± 0.9*	-	-	22.5 ± 5.2*	-	-	857 (125-1580)	-	-	26.4 ± 9.0
Peraza et al.2017 [81]	30	62	37	-	64.1 ± 7.9	62.8 ± 10.8	70.4 ± 9.1	-	ON	29.4 ± 0.88*	29.0 ± 0.9*	28.2 ± 1.5*	-	147.1 ± 112.0	201.6 ± 155.8	-	24.6 ± 10.4	28.9 ± 11.0	
Possin et al.2013 [74]	15	-	6	6	72.9 ± 5.2	-	73.9 ± 5.9		UPDRS OFF fMRI ON	NR	-	23.0 ± 4.8°		-	665 ± 343		-	30.8 ± 14.5	
Rektorova et al. 2012 [49]	18	18	-	14	60.9 ± 6.7	63.5 ± 9.1	-	72.4 ± 5.9	ON	29.5 ± 0.7*	29.6 ± 0.8*	-	23.2 ± 2.6*	696 ± 430.4	-	925.5 ± 412.0	NR	-	NR
Shin et al.2016 [86]	-	15	16	-	-	65.7 ± 6.4	69.1 ± 7.2	-	NR	-	28.6 ± 1.2	26.3 ± 1.5	-	0.0 (0-0)	0.0 (0-360)	-	19.1 ± 8.3	25.4 ± 8.8	-
Zhan et al.2018 [85]	9	9	9	9	70.0 ± 5.9	69.6 ± 7.8	68.4 ± 5.9	74.0 ± 5.1	UPDRS ON fMRI NR	26.7 ± 1.2°	27.0 ± 0.9°	21.9 ± 2.4°	14.1 ± 3.1°	630 ± 270	718 ± 372	721 ± 182	28.9 ± 10.5	33.1 ± 11.6	37.0 ± 12.1
Total sample size; mean age, global cognition, LEDD & UPDRS-III	353	289	222	68	64.5	63.6	66.9	71.5		28.7	28.3	26.1	21.2	468.3	564.9	716.9	18.0	21.6	25.7

UPDRS-III: Unified Parkinson's disease rating scale part III. LEDD: Levodopa equivalent daily dose. MMSE: Mini-mental state examination. MoCA: Montreal cognitive assessment. NR: Not reported.
[1] Values are mean ± standard deviation (SD), except for Gorges et al. (2015): mean (IQ range) and LEDD data from Shin et al. (2016) and Peraza et al. (2015): median (range).

Table 2
Experimental design of the included studies.

	fMRI	Criteria for PD-MCI	Criteria for PDD	Number of foci		Analysis	GSR	Software	AC
				Contrast HC vs. PD-CI	Contrast PD-CU vs. PD-CI				
Amboni et al., 2015 [73]	3T	MDS Task Force criteria, Level I [126]	–	4	–	ICA	Yes	Brain-Voyager QX	No[a]
Baggio et al., 2015 [75]	3T	MDS Task Force criteria, Level I [126]	–	6	3	ICA	No	FSL, AFNI	Yes
Bezdicek et al., 2018 [82]	3T	MDS Task Force criteria, Level II [126]	–	3	2	WBA	No	SPM12, ECM	No[b]
Borroni et al., 2015 [77]	1.5T	–	MDS Task Force criteria [127]	1	–	WBA	No	REST, SPM8	Yes
Canu et al., 2015 [76]	3T	MDS Task Force criteria, Level II [126]	–	13	–	ICA	No	FSL	No[a]
Chen et al., 2015 [78]	3T	–	MDS Task Force criteria [128]	4	4	SBA	Yes	REST, SPM8	No
Chen et al., 2017 [83]	3T	MDS Task Force criteria, Level I [126]	–	5	6	SBA	No	REST, SPM8	Yes
Díez-Cirarda et al., 2018 [84]	3T	MDS Task Force criteria, Level II [126]	–	11	–	ICA	No	CONN, GIFT, BCT	No
Gorges et al., 2015 [52]	3T	MDS Task Force criteria, Level I [126]	NR	13	34	SBA	No	TIFTSP, MATLAB	Yes
Hou et al., 2016 [80]	3T	MDS Task Force criteria, Level II [126]	–	22	2	SBA	No	REST, SPM8	Yes
Madhyastha et al., 2015 [48]	3T	Estimated decline from premorbid abilities.		4	–	ICA	No	FSL, AFNI, FreeSurfer	No
Peraza et al., 2015 [79]	3T		MDS Task Force criteria [127]	44	–	SBA	No	FSL 5.0, SPM8	Yes
Peraza et al., 2017 [81]	3T	MDS Task Force criteria, Level II [126]	–	3	19	ICA	No	FSL, REST	No
Possin et al., 2013 [74]	3T	NR	NR	48	–	WBA	No	SPM8, REST	No
Rektorova et al., 2012 [49]	1.5T	–	NR	2	–	SBA	No	SPM5	No
Shin et al., 2016 [86]	3T	MDS Task Force criteria, Level I [126]	–	–	35	SBA	Yes	REST, SPM8	No[a]
Zhan et al., 2018 [85]	3T	MDS Task Force criteria, Level I [126]	MDS Task Force criteria [127]	–	3	SBA	No	SPM8, REST	No
Total				183	108				

ACE-R: The Addenbrooke's Cognitive Examination Revised, NA: Not applicable, GSR: Global signal regression, AC: Atrophy correction, ICA: Independent component analysis, WBA: Whole brain analysis, SBA: Seed-based analysis, NR: Not reported.

[a] Instead of entering the subjects' GM volume maps as a voxel-wise regressor in intergroup comparison, a voxel-based morphometry was conducted and no significant differences were found between HC and PD-CI.

[b] A voxel-based morphometry showed no significant differences between PD-MCI and PD-CU. However, significant differences were found comparing HC with PD-MCI.

Table 3
Clusters of voxels with significant intergroup functional connectivity differences.

Contrast	Neural region	Side	MNI coordinates			Voxels	P-value	SDM-Z
			X	Y	Z			
HC > PD-CI	Rolandic operculum, BA 48	Right	44	−24	16	1363	0.00002	−2.705
	Inferior parietal gyri, BA 40	Left	−38	−42	52	1400	0.00004	−2.565
	Angular gyrus, BA 39	Right	48	−58	42	327	0.00089	−2.159
	Parahippocampal gyrus, BA 37	Left	−28	−34	−14	260	0.00025	−2.328
	Calcarine fissure/surrounding cortex, BA 23	Right	6	−60	16	161	0.00056	−2.221
	Superior frontal gyrus, dorsolateral, BA 9	Right	24	38	40	104	0.00056	−2.220
	Precentral gyrus, BA 4	Right	54	−2	36	67	0.00124	−2.114
	Precentral gyrus, BA 6	Right	38	−8	56	63	0.00143	−2.093
PD-CI > HC	Supramarginal gyrus, BA 40	Right	38	−32	38	277	~0	1.243
PD CU > PD-CI	Precuneus, BA 7	Left	−4	−60	42	931	~0	−2.312
	Median cingulate/paracingulate gyrus, BA 24	Right	4	2	34	261	0.00051	−1.820
	Superior frontal gyrus, dorsolateral, BA 10	Left	−22	64	14	191	0.00022	−1.939
	Precentral gyrus, BA 4	Right	56	−2	38	53	0.00214	−1.620
PD-CI > PD CU	Cerebellum, hemispheric lobule VI, BA 37	Right	30	−58	−20	1083	0.00029	1.371

Voxel threshold $p < 0.005$, peak height threshold: peak SDM-Z > 1.000, extent threshold: cluster size ≥10 voxels.

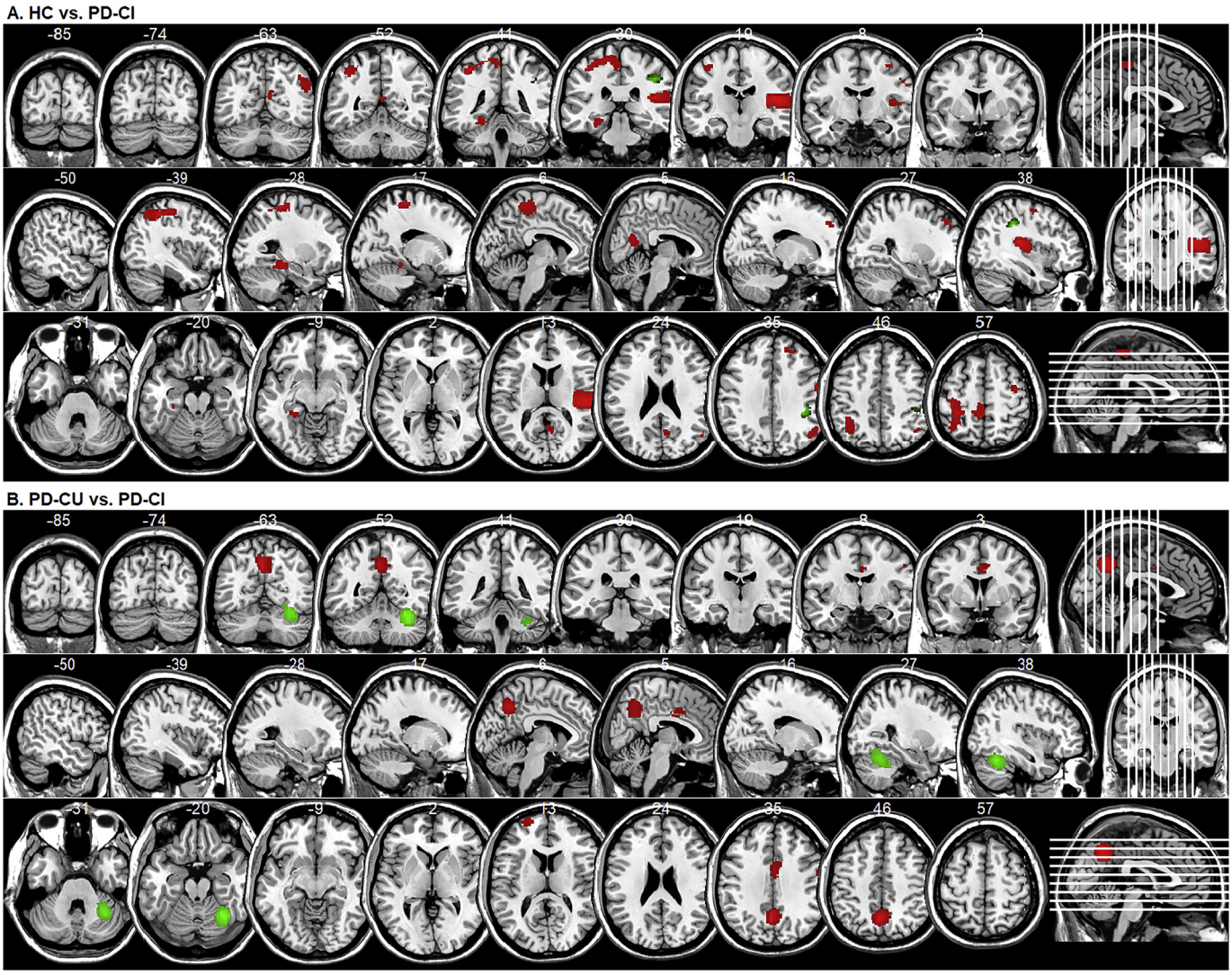

Fig. 2. Statistically significant effects of voxel-based meta-analysis for HC vs. PD-CI [A] and PD-CU vs. PD-CI [B]. Decreased functional connectivity in PD-CI is indicated in red and increased connectivity in PD-CI is indicated in green for all contrasts. Voxel threshold $p < 0.005$, peak height threshold: peak SDM-Z > 1.000, extent threshold: cluster size ≥10 voxels. x,y,z-coordinates of axial, sagittal and coronal slices are indicated in white. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

related to the motor symptoms of patients with PD. For the comparison of PD-CU with PD-CI, we detected a reduced connectivity specifically in the default mode network. After varying results in previous studies, our findings provide a more definite step in the differentiation of network disruptions associated with cognitive impairment in PD.

The default mode network is believed to serve an important role in various cognitive functions. It includes the medial parietal, bilateral inferior-lateral-parietal and ventromedial frontal cortex [69]. In healthy populations, reduced default mode network connectivity is associated with decreased memory performance, but also slower processing speed and decreased executive function [87–89]. In addition, alterations of the default mode network have been described in several other neurodegenerative disorders such as Alzheimer's disease, Huntington's disease and frontotemporal dementia [90–93]. Also in Parkinson's disease, changes in default mode network connectivity have been previously reported by several studies [94–96]. A recent meta-analysis of Tahmasian et al. (2017) investigated the resting-state functional connectivity in Parkinson's disease patients which were not selected specifically on the basis of cognitive performance. They similarly found an alteration in regions connected to the default mode network [97]. The authors concluded that this could be related to dysfunction of perception and executive functions in the PD patients. This supports our finding that the default mode network seems to be involved in cognitive decline in PD.

Besides the default mode network, we also found a notable decrease of functional connectivity in the auditory network of PD-CI when compared to HC. This network consists of the superior temporal gyrus, Heschl's gyrus and the posterior insular region [69]. The auditory network is not as well studied as the default mode network in PD. So far, only one study has reported functional connectivity changes in this network in PD patients [98]. It has also been described that, compared to age matched controls, PD patients show greater difficulty in hearing spoken words [99]. Furthermore, a correlation between CI and changes in auditory evoked potentials in PD has been reported by Nojszewska et al. (2009). The authors conclude that evaluation of the auditory evoked potentials may even serve as an indicator for CI in PD [100]. Thus, although disruption of this network may not necessarily cause CI, these changes in the auditory network could point to hearing-loss as a potential risk factor for CI in PD as has been suggested for dementia in the aging population [101]. However, only few studies have reported results about this network and in our meta-analysis this outcome was not preserved within the contrast of PD-CU with PD-CI. Therefore this outcome should be interpreted carefully. Based on our results it is also possible that disturbances in the auditory network are related to Parkinson's disease, but not specifically to cognitive impairment.

With respect to the fronto-parietal network, several studies have reported disruptions in the fronto-parietal network in PD patients with CI [53,102,103]. The fronto-parietal network seems to serve an important role in attention control [104]. While we hypothesized to find differences in functional connectivity of this network in PD-CI as compared to HC and PD-CU, our meta-analysis did not show this as convincingly as expected. Only for the peak coordinates of the contrast HC vs. PD-CI, a weak spatial correlation was found with this network. Since this association was not found for the PD-CU vs. PD-CI contrast, while the connection with the default mode network became more explicit in this second comparison, a more significant role for the default mode network in cognitive impairment in PD is implicated.

Interestingly, the AES-SDM analysis also revealed patterns of increased functional connectivity when comparing PD-CI patients with HC, in particular in the right supramarginal gyrus. Furthermore, an increased connectivity was also found in the right cerebellum for the contrast of PD-CI vs. PD-CU. It has been postulated that higher cortical functional connectivity in PD patients in the early stages of the disease, may reflect a compensatory mechanism to counteract slowly progressing CI [105]. The ability of brain areas to display compensatory overactivation was first suggested by Reuter-Lorenz et al. (2008) [106]. Based upon PET CT observations, several studies have also reported such compensatory mechanisms in PD patients [107,108]. It has also been described that loss of compensatory hyperactivation is associated with a worse performance on cognitive tasks [109]. This hypothesis may form an explanation for the observed increased functional connectivity in this meta-analysis. However, it is important to note that our robustness analysis indicated that the peak coordinate in the right supramarginal gyrus was driven by the studies of Chen et al. (2017) and Madhyastha et al. (2015), while the increased connectivity in the right cerebellar area was based solely on the study of Chen et al. (2015) and Chen et al. (2017). Because both peak coordinates were driven by only two studies these results must be interpreted cautiously.

Given the consistent involvement of the default mode network, our results suggest this network may hold promise as a biomarker for CI in PD patients, though further research is warranted. PD is thought to be a complex and heterogenic disease, probably with several different subtypes and changes over time [110,111]. For example, as stated in the introduction section, the dual syndrome hypothesis suggests that there are at least two PD subtypes, which among other things display a different profile of cognitive characteristics and a dissimilar degree of cognitive deterioration [15]. This makes it more complex to determine a specific pattern of functional connectivity alterations in PD with CI [112]. Therefore, deep phenotyping in longitudinal cohort studies, combining fMRI with other biomarkers such as structural imaging, genetic and clinical characteristics and cerebrospinal fluid biomarkers, would allow to further define specific fMRI correlates underlying the various phenotypes of the disease [113]. A number of studies performing multivariate analysis combining multi-modal neuroimaging techniques support the idea that Parkinson's disease is caused by a network-spread pathophysiology affecting several networks, including the default mode network, that correlate with cognitive deficits in PD [114–116]. Moreover, Long and colleagues (2012) developed a method which discriminated PD patients from HC with a power of 86.96% based on the combination of both structural and functional MRI characteristics [117]. The results of these studies support the promising future role of fMRI as a biomarker for PD.

As implicated by the multi-variate analysis described above, a relationship seems to exist between age-related brain atrophy in the healthy population and functional MRI activity of the brain [118]. For this reason, the application of brain atrophy corrections in fMRI studies in the PD population is important to avoid misleading results. However, in a considerable number of the studies included in our meta-analysis brain atrophy was not taken into account. Since our PD groups with cognitive decline showed a higher mean age when compared to the HC and PD-CU group, it cannot be ruled out that this might have influenced the meta-analysis to some extent.

This study has several other limitations. First, the study is limited by the small to moderate amount of studies and a certain level of heterogeneity in study characteristics. As demonstrated in Table 2, a variety of statistical or imaging methods, software packages and threshold settings were used in the included studies, which may have influenced our study results [119]. Specifically the inclusion of studies with different types of analytical methods (e.g. region of interest versus whole brain, or seed-based versus ICA) may introduce a bias in study results towards specific regions of interests. A meta-analysis using only studies applying a whole-brain analysis would give more conclusive results. Our analysis could therefore be seen as an exploratory study, which provides an indication of the results, while waiting for more conclusive results in the future. We suggest the validation of our findings in future studies consisting of an independent, methodologically homogeneous data set. Furthermore, sleeping during the acquisition has been shown to potentially increase functional connectivity in resting-state fMRI [120]. Unfortunately, only three of the included studies verified whether the subjects remained awake during the acquisition of the resting-state fMRI. Another major point of concern is that the fMRI was performed in 'ON' medication state as well as and in 'OFF' medication states among

the studies included in the meta-analysis. Eleven studies completed the MRI procedure while patients were 'ON' medication, three studies performed the fMRI in 'OFF' status and three studies did not report if the patients were 'ON' or 'OFF' dopaminergic medication during the scanning procedure. Although most studies acquired the fMRI data after patients took their dopaminergic medication, this heterogeneity can still lead to misleading results, since dopaminergic medication influences brain connectivity patterns both in a linear and non-linear way [42,121]. More specifically, this effect has also been described in the default mode network [122,123]. Although these effects are particularly relevant for intra-individual differences we cannot rule out that the meta-analysis is influenced by this dissimilarity in study characteristics. For this reason, further studies with homogeneity regarding the dopaminergic status of the PD patients are necessary to validate our results. Finally, diversity in the definition of MCI is another concern and although agreement on the diagnostic criteria has been formulated [124–128] there is no consensus yet and the cut-off scores for mild cognitive impairment are still ranging between −1 SD and −2 SD. In this meta-analysis, different criteria were allowed for MCI in the included studies (Table 2). Unfortunately, due to the limited number of included articles, we were not able to perform further subgroup analysis.

In conclusion, this meta-analysis reveals specific resting-state network disruptions in PD patients with CI, especially in the default mode network. Quantification of these network connectivity changes could serve as a biomarker for CI in PD and as such may be helpful in unravelling its pathophysiology. However, future studies with methodologically homogenous data sets, preferably combining different biomarkers in larger samples are necessary to confirm these outcomes and to further explore the potential role of fMRI as a biomarker for CI.

Declarations of interest

None.

Funding sources for study

None.

Author contributions

Conception and organization of the research project: AW, SW, AL, AD, HJ, MK. Execution of the search and article selection: AW, SW, HJ, MK. Design of the statistical analysis: AW, SW, HJ, MK. Execution of the statistical analysis: AW. Review and Critique of the statistical analysis: SW, HJ, MK. Writing of the first draft: AW. Review and critique on the manuscript: SW, HJ, AL, AD, MK. Final approval for submission: AW, SW, AL, AD, HJ, MK.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2018.12.016.

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