



Imaging executive functions in Parkinson's disease: An activation likelihood estimation meta-analysis

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ABSTRACT

Introduction: Executive dysfunction is a common and early cognitive symptom in Parkinson's disease (PD) with a detrimental effect on quality of life of patients and their care givers. Thus, a number of neuroimaging studies investigated the underlying neural correlates of such an impairment. Results of individual studies, however, are not univocal in terms of location and directionality of associated functional brain changes.

Objective: To assess convergence of abnormal brain activation in patients with PD during the performance of tasks probing executive functions (EF).

Methods: We screened the functional imaging literature on EF in PD using the PubMed database, extracted reported stereotactic data and tested for convergence of deviant neural activation in patients with PD when compared to healthy controls (HC) using a coordinate-based activation likelihood estimation approach.

Results: We identified 22 eligible papers from which the main proportion was targeted at the investigation of working memory encompassing 354 patients and 306 HC. Surprisingly, no significant converging aberrant activation between HC and patients (ON, OFF or ON + OFF medication, respectively) could be observed when controlling for multiple comparisons using family-wise error correction on cluster-level.

Conclusion: We conclude that there is currently not enough available evidence to pinpoint a specific neural correlate associated with executive dysfunction in PD. This might be due to the small number of studies performed and their methodical inconsistency. Therefore, it is important to conduct more research regarding functional brain changes associated with EF in these patients using more consistent frameworks and bigger samples.

1. Introduction

Cognitive impairment is a common feature of Parkinson's disease (PD), which greatly diminishes the patients' quality of life [1]. An early and frequently reported cognitive symptom is an impairment of executive functions (EF) including working memory (WM) [2]. EF and WM are umbrella terms which comprise a number of cognitive processes important for higher cognition [3]. Difficulties in these functions may, much like typical PD-associated motor symptoms, arise from the lack of dopamine within the dorsal striatum. Since EF rely on networks between the dorsal striatum and frontal areas such as the dorsolateral prefrontal cortex (dlPFC), it is hypothesized that disruptions of these

circuits will ultimately lead to impairments of frontal lobe functions resembling cognitive impairment observed in patients with frontal lobe damage [4]. In addition, it has been suggested that dorsal striatal dopamine depletion may be compensated for by relatively upregulating dopamine levels in the PFC itself, which has also been shown to influence cognitive performance [5]. Considering this, one may hypothesize that patients deprived of their dopaminergic medication and experiencing executive dysfunction may show diminished neural activation in fronto-striatal networks between dorsal striatum and dlPFC. Moreover, one might speculate that neural activation may be increased in relatively preserved regions of the brain, especially frontal areas, as a mechanism of compensation for poor dorsal striatal function or as a

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Abbreviations	
ALE	activation likelihood estimation
cFWE	family-wise error correction on cluster level
dIPFC	dorsolateral prefrontal cortex
EF	executive functions
fMRI	functional magnetic resonance imaging
HC	healthy controls
IPL	inferior parietal lobe
MNI	Montreal Neurological Institute stereotactic space
PD	Parkinson's disease
PD_ON	patients with Parkinson's disease ON dopaminergic medication
PD_OFF	patients with Parkinson's disease OFF dopaminergic medication
PET	positron emission tomography
PFC	prefrontal cortex
PRISMA	preferred reporting items for systematic reviews and meta-analyses
TAL	Talairach stereotactic space
TFCE	threshold-free cluster enhancement
UPDRS	unified Parkinson's disease rating scale
WM	working memory

consequence of pharmacological therapy.

However, results of neuroimaging studies investigating EF in patients with PD are relatively inconsistent with respect to location and directionality of pathological functional changes. Whereas some studies indicate that the striatal deficit during executive processing is located in the caudate nucleus [6], others observed an abnormality in the putamen [7], whereas some studies do not report abnormal processing within the striatum at all [8]. This inconsistency may be due to the rather vague concept of EF per se, but is further complicated by the use of various experimental paradigms in order to isolate and measure the specific underlying cognitive process. The question arises if a common neural substrate of executive dysfunction in PD can be identified.

To enable generalization across different experimental designs aiming to investigate EF and various patient cohorts, utilizing co-ordination-based quantitative meta-analysis can be helpful. Based on activation likelihood estimation (ALE), this approach integrates the reported coordinates of activation maxima from published studies in order to identify regions of significant converging activation [9]. This approach yields two major advantages: Firstly, we are able to take a “bird’s-eye view” on functional differences regarding EF between patients and HC independent of a specific task and secondly, the possibility to study a much greater sample size.

Thus, the objective of this meta-analysis is to integrate existing data from functional imaging studies related to EF in PD aiming to investigate whether a common neural substrate of abnormal functional activation can be identified using the ALE method. Since EF seem to be strongly influenced by dopamine levels, we conducted an analysis between HC and patients pooling across all patients regardless of medication state, and subsequently between HC and patients ON and OFF dopaminergic medication separately.

2. Methods

2.1. Literature search and study selection

A literature search was conducted on the Pubmed database (www.pubmed.org) according to recommendations from the PRISMA statement [10] using the search strings: “Parkinson’s disease” or “Parkinson disease” AND “fMRI” or “functional MRI” or “functional magnetic resonance imaging” or “task-based MRI” or “PET” or “positron emission tomography” AND “executive” or “planning” or “working memory” or “short term memory” or “set-shifting” or “switching”. Similar search terms have been shown useful in earlier work aiming to summarize and review the available *behavioral* literature on executive dysfunction in

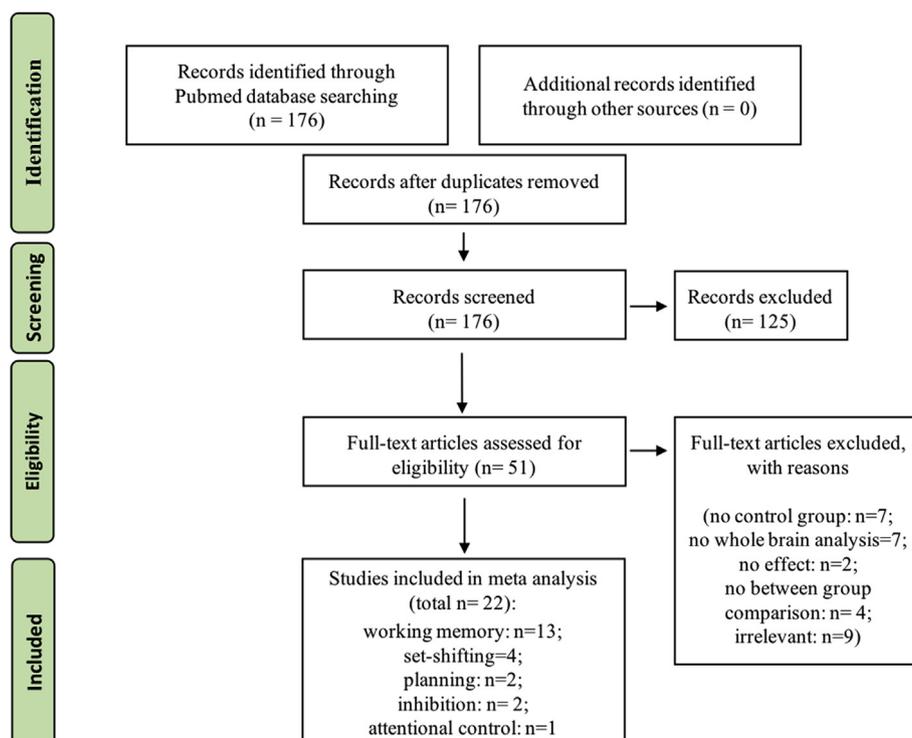


Fig. 1. Study selection flow chart.

PD [11]. A search on January 4th 2017 resulted in 176 articles, which were screened for eligibility (see Fig. 1). Review articles, case reports and editorial letters were excluded, but references of reviews were tracked for additional papers. We included original, cross-sectional articles, if they fulfilled the following criteria:

- written in English
- comparing PD patients (ON or OFF medication) vs. HC or PD patients ON vs. OFF medication during an EF challenge
- the analysis covered the “whole” brain (as opposed to specific regions of interest)
- imaging contrasts were defined as task vs. baseline or control task
- peak coordinates were reported in standard stereotactic space

2.2. Data extraction

From all eligible studies, information on the first author's name, year of publication, imaging modality (fMRI or H₂O-PET), number and age of subjects, type of EF task and number of reported foci were extracted. For patients with PD we additionally recorded medication state during scanning (ON or OFF) and, if provided, scores from the Unified Parkinson's Disease Rating Scale part III (UPDRS-III) (see Table 1). Peak coordinates (x,y,z) were extracted and, if needed, converted to MNI space coordinates for analysis [12]. Different experiments derived from one study were coded according to recommendations by Turkeltaub and colleagues [13] in order to minimize within-experiment and between-group effects.

2.3. Activation likelihood estimation based meta-analysis approach (ALE)

We used the revised version of the ALE approach [9] executed in SPM8 (<http://www.fil.ion.ucl.ac.uk/spm>) and implemented in

MATLAB version R2015a (<https://mathworks.com>). Using ALE gives the possibility to test whether peak activations reported in standard coordinates by published studies significantly converge in certain locations or if these locations are randomly distributed (i.e. the null hypothesis holds true). Details on the ALE algorithm have been described elsewhere [9,13]. In essence, spatial 3D Gaussian probability distributions are modelled around the peak coordinates of significant activation foci from different experiments. The term “experiment” in this context refers to the specific contrast of interest, e.g. PD_ON vs. HC, therefore one study can add several experiments to the ALE analysis. Our analysis encompassed comparisons between HC and patients with PD (ON, OFF and pooled ON + OFF medication, respectively) as well as between patients ON and OFF medication during the performance of an EF task contrasted with a control task or baseline. The width of the aforementioned probability distribution depends on the number of subjects from which a certain contrast was derived, in order to account for uncertainty associated with each focus due to variations in e.g. subjects, sample size or data processing and analysis [14]. Probabilities for all foci of one experiment are then combined into an overall activation map and voxel-by-voxel ALE scores are computed from the union of all activation maps indicating the convergence over all entered coordinates (i.e. all experiments of all studies). Finally, it is tested whether activations are randomly distributed or if there is significant converging activation using a family-wise error corrected threshold of $p < .05$ on cluster level (cFWE) [15]. If no significant converging activation could be observed, sensitivity of detection was increased using the threshold-free cluster enhancement (TFCE) method for exploratory purposes [16]. Clusters exceeding a minimum of 10 voxels are reported and anatomical location of the peaks were determined using the SPM Anatomy toolbox [17].

Table 1

Studies included in ALE meta-analysis sorted by tested function and alphabetical order.

Study	Task Modality	# PD	# HC	Age PD [years]	Age HC [years]	UPDRS-III OFF	UPDRS-III ON	Status	# Foci	
Working Memory										
Caminit et al., 2015 [1]	2-back	fMRI	13	12	63.3 ± 6.3	59.0 ± 2.3	n/a	n/a	ON	9
Cools et al., 2002 [2]	Spatial sequence Reproduction	PET	11	6	57.8 ± 2.5	58.0 ± 2.3	n/a	n/a	ON/OFF	7
Ekman et al., 2012 [3]	2-back	fMRI	77	24	67.6 ± 9.8	67.9 ± 6.8	24.3 ± 10.2	n/a	ON	25
Grossman et al., 2003 [4]	Sentence comprehension	fMRI	7	9	71.0 ± 10.2	65.7 ± 10.2	n/a	n/a	ON	9
Harrington et al., 2011 [5]	Time perception task with WM component	fMRI	21	19	67.0 ± 9.4	64.6 ± 8.5	29.6 ± 10.4	22.2 ± 8.0	OFF	19
Marié et al., 2007 [6]	Brown-Peterson paradigm	PET	8	9	59.6 ± 8.1	54.1 ± 13.5	n/a	n/a	ON	4
Mattay et al., 2002 [7]	2-back	PET	10	–	55.0 ± 2.6	–	8.8 ± 2.6	5.0 ± 1.8	ON/OFF	13
Passamonti et al., 2013 [8]	Match-to-sample task	fMRI	12	12	59.6 ± 6.8	60.2 ± 7.3	21.5 ± 8.4	12.3 ± 4.2	ON/OFF	7
Poston et al., 2016 [9]	Sternberg WM task	fMRI	24	23	65.3 ± 8.8	61.2 ± 10.1	32.9 ± 11.3	17.5 ± 10.5	ON/OFF	18
Rottschy et al., 2013 [10]	Finger tapping from memory	fMRI	23	23	67.2 ± 6.2	65.0 ± 4.4	n/a	23.9 ± 16.1	ON	63
Trujillo et al., 2015a [11]	3-back	fMRI	16	35	58.3 ± 9.5	55.5 ± 9.5	21.6 ± 9.0	n/a	De novo	13
Owen et al., 1998 [12]	WM task based on Tower of London task	PET	6	6	60.1 ± 2.6	57.7 ± 2.2	n/a	n/a	OFF	7
Ventre-Dominey et al., 2014 [13]	Object identification and spatial location task	PET	13	11	54.6 ± 6.7	53.2 ± 7.1	39.0 ± 10.3	9.1 ± 2.6	OFF	35
Set-shifting										
Gerrits et al., 2015 [14]	Switching between two sets of rules	fMRI	18	35	59.0 ± 10.0	56.0 ± 10.0	22	n/a	De novo	7
Jubault et al., 2009 [15]	Wisconsin card sorting task	fMRI	11	–	63.9 ± 7.3	–	29.5 ± 4.5	19.2 ± 5.0	ON/OFF	5
Monchi et al., 2006 [16]	Montreal card sorting task	fMRI	7	7	62	51.1	n/a	n/a	OFF	27
Monchi et al., 2004 [17]	Wisconsin card sorting task	fMRI	8	9	56.6	54.0	12.3	n/a	OFF	18
Planning										
Dagher et al., 2001 [18]	Tower of London task	PET	6	6	60.6 ± 8.8	58.6 ± 9.7	n/a	n/a	OFF	30
Trujillo et al., 2015b [19]	Tower of London task	fMRI	14	19	60.2 ± 8.9	58.4 ± 9.7	n/a	27.3 ± 7.8	ON	2
Inhibition										
Baglio et al., 2011 [20]	Go/No-Go task	fMRI	15	11	66.5 ± 6.4	66.9 ± 5.7	n/a	21.5 ± 7.2	ON	13
Farid et al., 2009 [21]	Go/No-Go task	fMRI	9	9	61.0 ± 8.6	59.0 ± 7.8	37.0 ± 5.0	11.0 ± 4.0	ON/OFF	11
Attentional control										
Boord et al., 2017 [22]	Attention network test	fMRI	25	21	66.0 ± 10.1	61.9	n/a	23.6 ± 8.7	ON	4

Age PD/Age HC = mean ± standard deviation [years], fMRI = functional magnetic resonance imaging; PET = Positron emission tomography; UPDRS = Unified Parkinson's disease rating scale; # Foci = number of reported activation peaks in study; # PD (female)/# HC (female) = number of subjects per group (number of female subjects), n/a = data not given, [1–22], = complete reference list provided in supplementary material.

3. Results

Twenty-two studies (16 fMRI and 6 H₂O-PET) were eligible for analysis with an average sample size of 16.1 ± 14.8 patients and 15.3 ± 9.1 HC (see Table 1 for details). Altogether these studies comprised 45 experiments conducted in 354 patients (mean age: 62.4 ± 5.3 years) and 306 HC (mean age: 58.1 ± 3.5 years). Exact number of experiments for each analysis are summarized in Table 2. For coordinate-based ALE computations including 17–20 experiments per contrast is suggested to ensure sufficient detection power [15]. For exploratory purposes however, we lowered the minimum number of contributing experiments for each comparison to 12. All comparisons comprised of fewer experiments were not analyzed.

From the 22 eligible papers the main proportion investigated WM (n = 13), whereas the remaining examined various aspects of EF (set shifting = 4; planning = 2; inhibition = 2; attentional control = 1). Therefore, we decided to conduct a second analysis exclusively with the studies using a WM paradigm. These 13 WM studies (8 fMRI and 5 H₂O-PET) had an average sample size of 18.5 ± 18.5 patients and 15.8 ± 9.0 HC and collectively comprised 27 experiments conducted in 241 patients (mean age: 62.8 ± 7.5 years) and 189 HC (mean age: 59.5 ± 3.9 years) (see Table 2).

3.1. Converging differential activation during tasks of executive functioning

Using cFWE correction, no significant converging activation in any of the investigated comparisons (PD_ON + OFF vs. HC, PD_ON vs. HC, PD_OFF vs. HC and PD_ON vs. PD_OFF) could be observed.

For exploratory purposes, we increased sensitivity by means of TFCE which resulted in a small cluster of converging aberrant activation in the right posterolateral pallidum [center: 28/-12/0 with size = 20 voxel], when comparing all patients (ON and OFF) with HC. This seemed mainly driven by the PD_OFF vs. HC comparison, since the same cluster was also found as diverging in this contrast (center: 28/-10/-1 with size = 100 voxel). In addition, the PD_ON vs. HC contrast revealed a small cluster of diverging activation in the left inferior parietal lobe (IPL) [center: -30/-52/56 with size = 18 voxel] (see Table 3).

3.2. Converging differential activation for working memory tasks only

When limiting the analysis to studies examining WM only, again no significant converging activation in the investigated comparison (PD_ON + OFF vs. HC) could be observed using cFWE correction.

However, after increasing sensitivity by means of TFCE, again a small cluster of aberrant activation in the right posterolateral pallidum could be observed when comparing patients with HC [center: 28/-12/-2; size = 27 voxel] (see Table 3).

4. Discussion

To our surprise, the ALE-based meta-analysis approach did not detect any consistent abnormal activation during the performance of EF tasks in patients with PD when compared to HC. Only in a subsequent analysis using TFCE, a small cluster of diverging neural activation could be observed in the right posterolateral pallidum which seemed to be driven by patients deprived of dopaminergic medication. When comparing HC to patients on dopaminergic medication, a small cluster of deviant neural activation was found in the left IPL.

When limiting the analysis to WM studies, a similar pattern only in the right posterolateral pallidum remained. Recent findings point to a vital role of the basal ganglia in certain aspects of EF, especially WM [18]. In particular, it has been suggested that the pallidum serves as “the bouncer in the brain” in charge of gating only task-relevant information into WM [19]. Moreover, this gating-mechanism is thought to be dopamine-dependent [20]. Notably, the functionally aberrant

cluster in the posterolateral pallidum was more pronounced when comparing patients deprived of dopaminergic medication with HC. Therefore one might speculate that this abnormality could be driven by dopamine depletion and be associated with the process of gating information into WM.

A second functionally aberrant cluster was observed in the left IPL. A similar meta-analysis in HC revealed that the medial and inferior parietal lobe were consistently activated during an n-back WM paradigm [21]. Especially the left IPL has been shown to play an important role in the phonological loop for storage of verbal information [22]. Furthermore, a functional discrimination between the ventral and dorsal IPL has been suggested with the dorsal fraction being especially active during high load conditions when attentional demands are high. Therefore, it has been hypothesized that the dorsal IPL, which encompasses the cluster of observed aberrant activity in our meta-analysis, “may support domain-general executive processes” [23]. Interestingly, clusters within the IPL have shown altered activation in previous ALE meta-analysis in PD, focusing on motor execution [24] and resting-state activity [25]. Tahmasian and colleagues identified a similar pattern in the IPL from resting-state data showing increased, supposedly compensatory, functional connectivity in off-state patients and decreased functional connectivity in patients on dopaminergic replacement therapy [25]. Due to limited power, our analysis does not allow drawing conclusions about the directionality of observed functional change. However, one interpretation of the altered IPL activity could be in terms of a compensatory mechanism counteracting dysfunction of the basal ganglia. Alternatively, it could reflect an over-dosed dopaminergic network since it was also evident in patients on dopaminergic replacement therapy.

However, the analysis using TFCE is only exploratory and results should be considered with great caution. Indeed, correcting for multiple comparisons using the cFWE method, as applied in our original analysis, has been recommended as the most appropriate way [15]. There might be several reasons for our negative result: Firstly, our analysis may have not been sufficiently powered to detect the hypothesized effect. Due to the limited number of eligible studies, some of our computations show relatively low statistical power, especially when the analysis was limited to WM. However, we are convinced that our negative result is not entirely explained by low power. The overall PD vs. HC comparison incorporated 32 experiments for the EF and 18 experiments for the WM analysis, which is above the recommended threshold for reliable ALE computations [15]. Alternatively, one might speculate that EF represent an extended functional network which is masked by additional, very variable task-specific activation. To investigate if such a network could in principle be detected using our approach, we additionally analyzed the HC data provided by these studies. Indeed, we observed two highly significant clusters in areas

Table 2
Number of experiments per contrast for analysis.

Comparison	Aberrant activation	Decreased activation	Increased activation
Executive functions			
PD_ON + OFF vs. HC	32	15	17
PD_OFF vs. HC	16	7'	9'
PD_ON vs. HC	16	8'	8'
PD_ON vs. PD_OFF	13	7'	6'
Working memory only			
PD_ON + OFF vs. HC	18	9'	9'
PD_OFF vs. HC	7'	3'	4'
PD_ON vs. HC	11'	6'	5'
PD_ON vs. PD_OFF	9'	5'	4'

HC = healthy controls, PD = patients with Parkinson's disease, PD_OFF = patients with Parkinson's disease OFF dopaminergic medication, PD_ON = patients with Parkinson's disease ON dopaminergic medication; ' = not analyzed.

Table 3
Significant converging activation differences between patients with PD and HC using TFCE.

Contrast	Neural region	side	MNI coordinates			size [voxel]	p
			x	y	z		
Executive functions							
PD vs. HC (32 experiments, 322 PD, 300 HC)	pallidum	right	28	−12	0	20	.012
PD_OFF vs. HC (16 experiments, 140 PD, 172 HC)	pallidum	right	28	−10	−1	100	.001
PD_ON vs. HC (16 experiments, 204 PD, 148 HC)	inferior parietal lobe	left	−30	−52	56	18	.028
Working memory only							
PD vs. HC (18 experiments, 235 PD, 189 HC)	pallidum	right	28	−12	2	27	.007

HC = healthy controls, PD = patients with Parkinson's disease, PD_OFF = patients with Parkinson's disease OFF dopaminergic medication, PD_ON = patients with Parkinson's disease ON dopaminergic medication; TFCE = threshold free cluster enhancement.

relevant to EF and WM, namely the supplementary motor area and dlPFC (see supplementary material: Fig. S1 and Table S1).

Another explanation could be that the anticipated effect might simply not be as strong and univocal as hypothesized previously. Studies using relatively small samples are susceptible to false positive (type I) errors and thus results from small samples with marginal significance should be considered with caution [26]. This might even be augmented when considering the possibility of publication bias in academic research. Indeed, it has been shown that significant findings are more likely to be published than non-significant results [27]. Consequently, the publicly available body of literature is inherently biased to positive findings. This could have led to an overestimation of the “true” executive impairment in PD on a behavioral and neuronal level. Of course our negative finding does not prove the absence of functional abnormalities associated with EF in PD. However, based on our result one might consider questioning whether the existing evidence thus far justifies the relatively undisputed claim of deficiencies in fronto-striatal loops resulting in the emergence of EF in PD.

But which other factors could explain the null-finding? Of course extensive variability in the underlying data may have prevented us from pinpointing an associated neural correlate. In research, data dredging to produce significant findings has been a matter of concern and only marginally significant effects could be the result of a particular hypothesis-driven analyses. In fact, the majority of studies contributing to this analysis reported results not corrected for multiple comparisons. Thus, when aiming to integrate these diverse findings using the ALE approach, high variability and consequently high levels of noise in the data could potentially cover the hypothesized effect.

Moreover, the experimental manipulations used in the integrated neuroimaging studies add substantial variability. When studying EF one should cautiously consider what experimental paradigm to use and which cognitive processes this task measures. Thus, it is of great importance to carefully design tasks that tap into the specific cognitive process of interest and aim to apply them consistently. Currently however, the here included 13 WM studies used 10 different WM paradigms.

In addition, studies vary greatly in terms of design, image acquisition, preprocessing and analysis including the use of various statistical thresholds. Moreover, study cohorts vary considerably regarding their medication status. Some studies are conducted with patients on dopaminergic medication, whilst others are conducted after withdrawal. Also, the medication withdrawal window to reach an off-state varied between 12 [28] and 72 h [7]. Considering which effect dopamine depletion as well as overdosing may have on EF and their underlying neural correlates, this is a major issue of concern. Finally, it has been shown that task performances are affected differently by dopaminergic medication depending on whether they rely more on dorsal or ventral striatum [29]. This interaction may add an additional layer of variability to the underlying data.

Next to these methodological differences, the cohorts studied ranged from de-novo to moderately affected patients, individuals with

or without MCI and patients with or without deep brain stimulation. Note, that the here included sample mainly comprised cognitively preserved patients. Previous reports, however, have shown that PD-MCI patients show more pronounced fronto-striatal deviations than patients with PD only [30]. Thus, one might speculate that a common pattern of abnormal activation during EF may only become evident at this advanced state.

Considering the sheer number of patients showing executive dysfunction in PD [2] and the great impact this has on the quality of life of those individuals [1], understanding these impairments and their underlying neural mechanisms is crucial. However, despite substantial efforts, the currently available neuroimaging evidence is not conclusive. Therefore, more studies with larger sample sizes are needed, which are focused on one particular aspect of EF (e.g., manipulation of information in WM) and harmonized with respect to sample characteristics (e.g., clinical stage) and study protocols (e.g., ON/OFF medication).

4.1. Limitations

As outlined above, the amount of brain imaging literature on EF in PD, which was eligible for inclusion, was rather low. Only 22 studies were included, from which not all comprised every comparison of interest (PD_ON vs. HC, PD_OFF vs. HC and PD_ON vs. PD_OFF). Therefore, some of the comparisons were close to the minimum number of recommended experiments [15]. For the same reason, our analysis was mostly limited to the investigation of “aberrant” activation rather than exploring the directionality of the observed functional changes.

4.2. Conclusion

In conclusion, using the ALE-based meta-analysis approach, we did not observe converging aberrant activation between patients with PD and HC during EF when correcting for multiple comparisons using cFWE. Importantly, this negative finding does not prove the absence of functional differences between patients with PD and HC, but may rather be the result of extensive methodological variability between relatively few studies. Therefore, it is important to conduct more research in the field of EF in PD and the associated underlying functional brain changes using more consistent frameworks and bigger samples.

Disclosures

Declarations of interest

None for all authors.

All authors have approved the submitted version of the manuscript.

Author contribution

(1) the conception and design of the study, or acquisition of data, or

analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

All authors: 1, 2 & 3.

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Appendix A. Supplementary data

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References

- [1] A. Kudlicka, L. Clare, J.V. Hindle, Quality of life, health status and caregiver burden in Parkinson's disease: relationship to executive functioning, *Int. J. Geriatr. Psychiatry* 29 (1) (2014) 68–76.
- [2] G. Dimberger, M. Jahanshahi, Executive dysfunction in Parkinson's disease: a review, *J. Neuropsychol.* 7 (2) (2013) 193–224.
- [3] A. Diamond, Executive functions, *Annu. Rev. Psychol.* 64 (2013) 135–168.
- [4] A.A. Kehagia, R.A. Barker, T.W. Robbins, Cognitive impairment in Parkinson's disease: the dual syndrome hypothesis, *Neurodegener. Dis.* 11 (2) (2013) 79–92.
- [5] D.E. Vaillancourt, D. Schonfeld, Y. Kwak, N.I. Bohnen, R. Seidler, Dopamine overdose hypothesis: evidence and clinical implications, *Mov. Disord.* 28 (14) (2013) 1920–1929.
- [6] O. Monchi, M. Petrides, B. Mejia-Constain, A.P. Strafella, Cortical activity in Parkinson's disease during executive processing depends on striatal involvement, *Brain* 130 (1) (2006) 233–244.
- [7] K.L. Poston, S. YorkWilliams, K. Zhang, W. Cai, D. Everling, F.M. Tayim, S. Llanes, V. Menon, Compensatory neural mechanisms in cognitively unimpaired Parkinson disease, *Ann. Neurol.* 79 (3) (2016) 448–463.
- [8] P. Boord, T.M. Madhyastha, M.K. Askren, T.J. Grabowski, Executive attention networks show altered relationship with default mode network in PD, *NeuroImage Clin* 13 (2017) 1–8.
- [9] S.B. Eickhoff, D. Bzdok, A.R. Laird, F. Kurth, P.T. Fox, Activation likelihood estimation meta-analysis revisited, *Neuroimage* 59 (3) (2012) 2349–2361.
- [10] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, *Ann. Intern. Med.* 151 (4) (2009) 264–269.
- [11] A. Kudlicka, L. Clare, J.V. Hindle, Executive functions in Parkinson's disease: systematic review and meta-analysis, *Mov. Disord.* 26 (13) (2011) 2305–2315.
- [12] J.L. Lancaster, D. Tordesillas-Gutiérrez, M. Martínez, F. Salinas, A. Evans, K. Zilles, J.C. Mazziotta, P.T. Fox, Bias between MNI and Talairach coordinates analyzed using the ICBM-152 brain template, *Hum. Brain Mapp.* 28 (11) (2007) 1194–1205.
- [13] P.E. Turkeltaub, S.B. Eickhoff, A.R. Laird, M. Fox, M. Wiener, P. Fox, Minimizing within-experiment and within-group effects in activation likelihood estimation meta-analyses, *Hum. Brain Mapp.* 33 (1) (2012) 1–13.
- [14] S.B. Eickhoff, A.R. Laird, C. Grefkes, L.E. Wang, K. Zilles, P.T. Fox, Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: a random-effects approach based on empirical estimates of spatial uncertainty, *Hum. Brain Mapp.* 30 (9) (2009) 2907–2926.
- [15] S.B. Eickhoff, T.E. Nichols, A.R. Laird, F. Hoffstaedter, K. Amunts, P.T. Fox, D. Bzdok, C.R. Eickhoff, Behavior, sensitivity, and power of activation likelihood estimation characterized by massive empirical simulation, *Neuroimage* 137 (2016) 70–85.
- [16] S.M. Smith, T.E. Nichols, Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference, *Neuroimage* 44 (1) (2009) 83–98.
- [17] S.B. Eickhoff, K.E. Stephan, H. Mohlberg, C. Grefkes, G.R. Fink, K. Amunts, K. Zilles, A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data, *Neuroimage* 25 (4) (2005) 1325–1335.
- [18] F. McNab, T. Klingberg, Prefrontal cortex and basal ganglia control access to working memory, *Nat. Neurosci.* 11 (1) (2008) 103.
- [19] E. Awh, E.K. Vogel, The bouncer in the brain, *Nat. Neurosci.* 11 (1) (2008) 5.
- [20] A.J. Gruber, P. Dayan, B.S. Gutkin, S.A. Solla, Dopamine modulation in the basal ganglia locks the gate to working memory, *J. Comput. Neurosci.* 20 (2) (2006) 153.
- [21] A.M. Owen, K.M. McMillan, A.R. Laird, E. Bullmore, N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies, *Hum. Brain Mapp.* 25 (1) (2005) 46–59.
- [22] G. Vallar, A.M. Di Betta, M.C. Silveri, The phonological short-term store-rehearsal system: patterns of impairment and neural correlates, *Neuropsychologia* 35 (6) (1997) 795–812.
- [23] S.M. Ravizza, M.R. Delgado, J.M. Chein, J.T. Becker, J.A. Fiez, Functional dissociations within the inferior parietal cortex in verbal working memory, *Neuroimage* 22 (2) (2004) 562–573.
- [24] D.M. Herz, S.B. Eickhoff, A. Løkkegaard, H.R. Siebner, Functional neuroimaging of motor control in Parkinson's disease: a meta-analysis, *Hum. Brain Mapp.* 35 (7) (2014) 3227–3237.
- [25] M. Tahmasian, S.B. Eickhoff, K. Giehl, F. Schwartz, D.M. Herz, A. Drzezga, T. van Eimeren, A.R. Laird, P.T. Fox, H. Khazaie, Resting-state functional reorganization in Parkinson's disease: an activation likelihood estimation meta-analysis, *Cortex* 92 (2017) 119–138.
- [26] K.S. Button, J.P. Ioannidis, C. Mokrysz, B.A. Nosek, J. Flint, E.S. Robinson, M.R. Munafò, Power failure: why small sample size undermines the reliability of neuroscience, *Nat. Rev. Neurosci.* 14 (5) (2013) 365.
- [27] F. Song, S. Parekh, L. Hooper, Y.K. Loke, J. Ryder, A.J. Sutton, C. Hing, C.S. Kwok, C. Pang, I. Harvey, Dissemination and publication of research findings: an updated review of related biases, *Health Technol. Assess.* 14 (8) (2010) 1–193.
- [28] T. Jubault, L. Monetta, A.P. Strafella, A.-L. Lafontaine, O. Monchi, L-dopa medication in Parkinson's disease restores activity in the motor cortico-striatal loop but does not modify the cognitive network, *PLoS One* 4 (7) (2009) e6154.
- [29] E. Aarts, A.A. Nusslein, P. Smittenaar, R.C. Helmich, B.R. Bloem, R. Cools, Greater striatal responses to medication in Parkinson's disease are associated with better task-switching but worse reward performance, *Neuropsychologia* 62 (2014) 390–397.
- [30] U. Ekman, J. Eriksson, L. Forsgren, S.J. Mo, K. Riklund, L. Nyberg, Functional brain activity and presynaptic dopamine uptake in patients with Parkinson's disease and mild cognitive impairment: a cross-sectional study, *Lancet Neurol.* 11 (8) (2012) 679–687.