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Functional MRI to Study Gait Impairment in Parkinson's Disease: a Systematic Review and Exploratory ALE Meta-Analysis

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Abstract

Purpose of Review Whilst gait impairment is a main cause for disability in Parkinson's disease (PD), its neural control remains poorly understood. We performed a systematic review and meta-analysis of neuroimaging studies of surrogate features of gait in PD.

Findings Assessing the results from PET or SPECT scans after a period of actual walking as well as fMRI during mental imagery or virtual reality (VR) gait paradigms, we found a varying pattern of gait-related brain activity. Overall, a decrease in activation of the SMA during gait was found in PD compared to elderly controls. In addition, the meta-analysis showed that the most consistent gait-related activation was situated in the cerebellar locomotor region (CLR) in PD.

Summary Despite methodological heterogeneity, the combined neuroimaging studies of gait provide new insights into its neural control in PD, suggesting that CLR activation likely serves a compensatory role in locomotion.

Keywords Parkinson's disease · Gait · Neuroimaging · Cerebellum · Activation of likelihood estimation · Meta-analysis

Introduction

Gait impairment is one of the main causes for disability in the daily lives of patients with Parkinson's disease (PD) [35]. Combined with postural instability, PD patients are at an exceptionally high risk for repeated falls, leading to a complex chain reaction of clinical consequences, including severe injuries, immobilisation and mortality [2, 4]. Even early in the disease course patients present with continuous gait problems, such as reduced step length with increased cadence and stride time variability, causing them to be at a higher risk for falls than their age-matched peers [21, 23]. Indeed, more than half of PD patients experience a fall within the first 3 years after clinical diagnosis [24]. As the disease progresses over time, often other more complex and episodic gait disorders appear, such as festination and freezing of gait [30], which further increase the risk of falling [23] and drastically reduce the quality of life for patients [40].

The pathophysiology underlying gait impairment in PD remains poorly understood. One of the main reasons is that gait control involves a complex interplay across multiple neural circuits that span cortical but also subcortical structures that cannot be directly imaged with ambulatory neuroimaging techniques. Some approaches such as electroencephalography (EEG) and near-infrared spectroscopy (NIRS) have provided some insights into gait disturbances [1•, 6, 8, 25, 32], but they lack neuroanatomical localisation. Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) are nuclear imaging techniques that provide whole brain activity coverage by measuring radiotracer uptake using gamma rays. The strength of these techniques is that they can assess the brain activations associated with actual gait tasks [19, 26, 37]. These techniques can also be used to study the neural control of gait in patients with metal implants, such as deep brain stimulators in PD [41]. Yet, PET and SPECT require the recording of activity usually after a period of gait has been undertaken, resulting in an 'estimate' of changes that might have been present during the task.

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Magnetic resonance imaging (MRI) is a safe technique that provides whole-brain coverage with the best spatial resolution and without requiring radioactive tracers. It can be used to study structural alterations in the brain (i.e. grey matter volumes and white matter connectivity) or changes in blood level oxygen level (BOLD) during the resting state or while performing functional tasks. Functional MRI (fMRI) has therefore often been the technique of choice for studying the neural correlates underlying complex human behaviours. However, the key difficulty of MRI is that subjects have to be in a supine position and lie absolutely still, thereby precluding the study of actual gait [8, 25].

The evidence that can be provided with resting state fMRI or structural MRI can only be indirectly related to gait by comparing groups with and without gait impairment or by correlating the imaging findings with gait measures obtained outside the scanner. However, in the last decade, researchers have developed methods that allow for the investigation of the neural mechanisms underlying surrogate measures of gait during fMRI [1•, 8, 25]. These include action simulation (i.e. motor imagery or action observation) of gait or motor execution of the lower limbs using various paradigms [1•, 5•, 8, 25, 29]. Action simulation can give rise to a comprehensive experience of gait that, despite the supine position, likely activates areas involved with postural control [33, 36]. On the downside, only proxy measures of gait-related output can be generated from action simulation paradigms to ascertain if subjects are truly engaged in action simulation of gait and to compare performance across subjects and groups. Thus, researchers started to study the neural correlates of virtual reality (VR) gait paradigms, which utilise foot tapping movements to navigate a three-dimensional environment during fMRI, under the assumption that bilateral coordination of the lower limbs and ankle dorsi- and plantar flexion are integral features of gait control [16, 29, 34]. The benefit of VR paradigms is that behavioural data of the subject's stepping performance can be generated and directly linked to the BOLD data obtained. With the addition of VR environments, the immersion in a gait-like experience can be further enhanced [5•]. The virtual environments also engage sensorimotor feedback mechanisms implicated in gait control. Finally, virtual environments can be adjusted to simulate the visual feedback obtained during a variety of common gait conditions. This is of particular interest for PD, as the virtual environments can simulate situations in which gait control often breaks down in real-life, such as during turning [15] or passing through doorways [27]. However, similar to other MR imaging paradigms, foot tapping in a supine position does not engage the postural and balance control circuits that are integrally involved in real-life walking [32] and impaired in PD [3].

Taken together, there has been a recent surge of evidence on the neural mechanisms underlying gait control in people with PD, which has great potential to guide treatment developments [17]. However, heterogeneity between task conditions and subjects across studies results in variable outcomes making it difficult to pinpoint the precise activation patterns that characterize altered gait control in PD. The aim of the present review was therefore to systematically summarize the outcomes of any task-based fMRI experiment and conduct an exploratory activation of likelihood estimation (ALE) meta-analysis to assess whether there are any convergent activation patterns that characterize gait control in PD, in comparison to gait control in healthy older adults.

Literature Searches

A systematic search without language or date restrictions was conducted in the electronic databases of Pubmed, Medline, Embase and Web of Science to identify relevant studies published until March 22nd 2019. For PD, the following search terms and their common abbreviations were used: (Parkinson disease AND (gait OR walking OR stepping OR freezing AND (Magnetic Resonance Imaging OR Positron-Emission Tomography OR Tomography, Emission-Computed, Single-Photon)), yielding a total of 892 non-duplicate hits. For healthy older adults, a similar search string was used after replacing "Parkinson disease" with (Aged AND (Healthy OR Community dwelling)), yielding a total of 365 non-duplicate hits. Titles, abstracts and full-texts were subsequently screened for inclusion and exclusion criteria.

Inclusion Criteria for the Systematic Overview

Peer-reviewed published articles in any language using PET, SPECT or fMRI were included if they studied the neural underpinnings of gait impairment in patients with idiopathic Parkinson's disease or healthy older adults (mean age ≥ 55 years). This included (i) studies using action simulation paradigms, such as motor imagery and action observation or studies investigating motor execution of the bilateral lower limbs with or without cueing or virtual reality paradigms; (ii) studies assessing radiotracer uptake after an actual gait task performed outside the scanner (PET, SPECT) or during scanning (SPECT); and (iii) studies using the above-named techniques to assess the effects of an intervention on the neural correlates of gait in PD.

Exclusion Criteria for the Systematic Overview

Non-peer reviewed articles, conference abstracts and reviews of the literature with or without meta-analysis, as well as animal studies were excluded. Studies using structural MRI, resting state fMRI, EEG, NIRS or non-invasive brain stimulation (e.g. transcranial magnetic stimulation), as well as resting state PET or SPECT studies without inclusion of the techniques described above to model gait, were also excluded.

Finally, passive movements of the lower limbs or unilateral foot tapping, as well as changes in optic flow without inclusion of the techniques described above were not considered as gait-specific and thus excluded from the review and meta-analysis.

The above-described screening led to a final inclusion of 23 studies on PD (Table 1) and 7 additional studies on healthy older adults (Supplementary materials). Key findings of this analysis are reported in Table 1, showing a great variety of gait-related brain activations, incorporating the frontal and parietal cortices and the cerebellum across groups. Furthermore, an altered activation of the SMA during gait was a consistent finding in PD. However, the great variety of gait-related brain activations hampers drawing firm conclusions. Therefore, a meta-analysis was performed to determine brain regions consistently activated during gait-like tasks across studies.

Inclusion and Exclusion Criteria for the Exploratory ALE Meta-analysis

From our initial systematic search, we selected experiments from studies that reported whole brain peak voxel coordinates in standard stereotactic space (i.e. MNI or Talaraich) for within-group comparisons, for both PD and controls, whereby 'gait' was taken as the condition of interest (e.g. motor imagery of gait > visual imagery of gait, foot tapping > rest). Contrasts between two similar gait conditions were included if the condition of interests was hypothesised to still engage gait-related areas. For intervention studies, only the baseline contrasts prior to the intervention were included. The number of included subjects in each experiment had to be reported as the ALE analysis controlled for the number of subjects in each experiment. Between-subject contrasts were excluded as to prevent comparisons across groups of unequal size and to limit between-subject variability [20••]. Finally, studies that only reported the outcomes of a region-of-interest analysis were also excluded.

Data Extraction and ALE Meta-analysis

In short, ALE is a coordinate-based meta-analysis technique that determines whether peak voxel activation coordinates (i.e. foci) across different experiments overlap at a statistical level (greater than expected by chance) by modelling them as 3D Gaussian probability distributions centred at the respective coordinates [10, 38]. The exploratory meta-analyses were performed using the revised version of the ALE algorithm that takes the number of subjects in each experiment into account [10, 11, 38]. We followed the methodology as described in detail by Hardwick et al. [20••]. For each experiment, the sample size, mean age, sex distribution of the subjects, contrast of interest and whole-brain peak-voxel coordinates in MNI or Talaraich space were extracted. Meta-analyses across all subjects, one across PD subjects only and one across healthy older adults were performed. In addition, contrasts between the resultant meta-analyses of PD and controls were conducted using random effects ALE subtraction analysis [11], as per Hardwick et al. [20••] and anatomically labelled in MNI space using the xjView software.

ALE-Sample Characteristics

Sixteen gait-related within-subject experiments totalling 161 peak voxel coordinates (i.e. foci) were included for PD and also 16 gait-related within-subject experiments, totalling 264 foci, were included for controls (Table 2). The outcomes of the meta-analysis are based on a total of 178 PD subjects (16.2 subjects on average per experiment; mean (SD) of the mean age = 65.5 (4.1); %males = 67.1%) and a total of 208 healthy older adults (16.0 subjects on average per experiment; mean (SD) of mean age = 67.3 (6.3), %males = 43.8%). There was no significant difference between the two cohorts on the average number of subjects per experiment (independent t test: $t = 0.07$, $p = 0.942$) or average age of the subjects in each experiment ($t = -0.75$, $p = 0.460$). A significant difference in sex distribution was found (Chi-square test: $\chi^2 = 19.0$, $p < 0.01$) with significantly more females in the control cohort. As we included < 20 experiments, which is condsidered the minimal number required to achieve sufficient power for moderate effects [12••], for both PD and controls, our ALE meta-analysis must be considered exploratory.

Exploratory ALE-Results

First, the spatial distribution of ALE z-scores across both groups was plotted without further statistical inference to ensure that a motor network would appear. The ALE scores represent the sum of modelled activations, whereby each foci has been replaced with three-dimensional Gaussian distributions with a width that was set according to the number of subjects in each experiment [10, 20••]. This exploration revealed an expected gait-related pattern of activations across the primary and pre-motor cortices, the visual cortex, basal ganglia, and the cerebellar and brainstem locomotor regions (Fig. 1a).

A cluster-level family wise error (cFWE) correction for multiple comparisons was applied when conducting the actual meta-analyses [12••]. Across both PD and healthy older adults, significant gait-related activations were found in the midline supplementary motor area (SMA, 281 voxels, peak voxel: − 2/− 4/66), the midline leg area of the primary motor cortex (M1, 359 voxels, peak voxel: − 8/− 32/66), the cerebellar locomotor region (CLR, 313 voxels, peak voxel: − 1/− 50/− 10) and right lateral cerebellar lobule VI/Crus-I (221 voxels, peak voxel at: 36/− 54/− 32) (Fig. 1b). Within the PD cohort,

Table 1 Systematic overview of included studies in PD

Study	Imaging technique	Sample	Age in years mean (SD)	Sex M/F	Med status	Task of interest	Analysis type	Key findings
Hanakawa, 1999a	SPECT.^{99m}Tc	10 PD 10 Con	67.0 (4.2) 67.0 (4.0)	6/4 6/4	OFF	Actual walking on a treadmill during scanning	Whole brain	Under-activation in left medial frontal area, right precuneus, left lateral cerebellum and over-activation in left temporal cortex, right insula, left cingulate and CLR.
Hanakawa, 1999b	SPECT.^{99m}Tc	10 PD 10 Con	68.0 (6.0) 67.0 (6.0)	6/4 5/5	ON	Actual walking on a treadmill with transverse visual cues vs. parallel visual cues during scanning	ROI	Transverse lines activated posterior parietal cortex and cerebellar hemispheres in both groups. PD further showed enhanced activation in right lateral premotor area with transverse cues compared to controls.
Ouchi, 2001	PET.^{11}C-CFT (DAT)	7 PD 6 Con	66.3 (6.6) 65.3 (5.9)	5/2 5/1	De novo	Actual walking in a corridor for 50mins followed by a resting state PET scan	ROI	In controls, ^{11}C-CFT uptake decreased in the putamen. PD showed no such reduction in the putamen, but a significant reduction in the caudate and orbitofrontal cortex.
Snijders, 2011 (#)	fMRI	24 PD 21 Con	60.2 (8.9) 57.0 (9.1)	15/9 12/9	OFF	MI of gait vs. VI or rest conditions in PD vs. Controls, and FOG vs. NF	Whole brain + ROI	MI of gait in PD increased activation in right SMA. Compared to rest, MI of gait increased activations in the CLR and striatum in both groups. FOG showed more activation in the MLR and decreased activation in mesial frontal and posterior parietal cortices compared to NF.
Crémers, 2012 (#)	fMRI	15 PD 15 Con	65.1 (9.5) 63.8 (8.1)	8/7 7/8	ON	MI of gait vs. MI of standing	Whole brain	In PD, MI of gait only activated the rostral SMA. Compared to controls, PD showed hypo-activations in the posterior parietal, cingulate, precuneus and lingual cortices, as well as in the left hippocampus, left lateral cerebellum and cerebellar vermis.
Wai, 2012*	fMRI	13 PD 13 Con 14 YA	63.5 (13) 64.8 (6.1) 21.5 (1.6)	7/6 7/6 7/7	OFF	AO + MI of gait including gait initiation, stepping over an obstacle and gait termination	Whole brain	**Only outcomes of group comparisons were reported (*i.e. *PD* vs. *controls).* No differences were found during gait initiation. AO + MI of stepping over an obstacle increased activations in the right dorsal premotor area, precentral, right inferior parietal lobule and bilateral precuneus in PD versus older controls. At gait termination PD activated visual areas more than older controls.
Peterson, 2013	fMRI	19 PD 20 Con	64.9 (7.6) 66.6 (7.6)	11/8 5/15	OFF	MI of simple (forward) and	ROI	PD showed reduced activity in the globus pallidus ROI across all tasks when compared to controls, and increased activation in the SMA during MI of turning compared to MI of forward or backward gait.
Shine, 2013a*	fMRI	14 FOG 15 NF	63.2 (7.0) 63.4 (8.3)	N.R.	OFF	Foot tapping + VR with high and low cognitive load task conditions	Whole brain + ROI	**Only high* vs. *low cognitive load contrast reported that excluded most gait-related activations.* FOG showed under-activation of pre-SMA, STN, insula and ventral striatum during high cognitive load compared to NF.
Shine, 2013b*	fMRI	18 FOG	66.8 (8.2)	18/0	OFF	Foot tapping + VR with FOG-provoking task conditions	Whole brain + ROI	**Only "freezing > stepping" contrast, that excluded most gait-related activations.* Freezing events were associated with reduced activations in the sensorimotor cortices, caudate, thalamus and globus pallidus and with increased activations in fronto-parietal cortical regions.
	fMRI	10 FOG	67.1 (6.4)	N.R.	OFF & ON		ICA	

Table 1 (continued)

Study	Imaging technique	Sample	Age in years mean (SD)	Sex M/F	Med status	Task of interest	Analysis type	Key findings
Shine, 2013c		10 NF	66.3 (6.2)			Foot tapping + VR with FOG- provoking task conditions		Patients with FOG showed functional decoupling between the bilateral basal ganglia and cognitive control networks.
Peterson, 2014	fMRI	9 FOG 9 NF	66.6 (6.7) 62.7 (8.5)	5/4 7/2	OFF	MI of simple (forward) and complex (turning, backward) gait vs. MI of standing	ROI	No difference was seen between simple and complex task conditions in both groups. During MI of gait FOG patients showed reduced activations in the right globus pallidus, the SMA, and MLR compared to NF.
Gilat, 2015	fMRI	17 FOG 10 NF	67.4 (6.2) 64.8 (4.1)	13/4 9/1	OFF	Foot tapping + VR of a straight corridor vs. 90 degree turns	Whole brain + ROI	Both FOG and NF showed activations across motor and visual cortices, cerebellum and MLR during foot tapping in the VR. FOG had lower activations in the left SMA and superior parietal cortex and increased activations in bilateral inferior frontal cortices when turning, as compared to NF.
Maillet, 2015 (#)	PET.H2^{15}O	8 PD 8 Con	63.3 (6.3) 62.9 (6.7)	4/4 4/4	OFF and ON	MI of gait vs. VI or a control task of simply watching a picture of the corridor used.	Whole brain	PD OFF activated the premotor and partietal cortices and MLR during MI of gait. PD ON activated the motor cortices, putamen, thalamus and cerebellum, while reducing activation in premotor and parietal cortices.
Tard, 2015	PET.^{18}FDG	11 FOG 11 NF	61.4 (4.8) 62.2 (3.4)	7/4 8/3	OFF	Actual walking a FOG provoking course for 30 min	Whole brain+ ROI	Gait in FOG was associated with reduced activations in the temporopolar, orbitofrontal and associative premotor cortices and with greater activations around the intraparietal sulcus of the paracentral lobule as compared to NF.
Weiss, 2015	PET.H2^{15}O	10 PD	N.R.	N.R.	OFF & ON	MI of gait vs. MI of standing	Whole brain	All patients had bilateral STN-DBS. Main effect of MI of gait (regardless of STN-DBS ON/OFF and dopamine ON/OFF) revealed increased activations in the SMA and right superior parietal lobule.
Maidan, 2016 (#)	fMRI	20 PD 20 Con	72.9 (1.6) 66.9 91.3)	14/6 10/10	ON	MI of gait with usual gait, obstacles and navigation conditions vs. a visual control task of watching the scenes without MI	Whole brain	Obstacle negotiation activated the occipital and middle frontal cortices and cerebellum compared to usual walking in both groups. PD showed increased activations in frontal, parietal, temporal and occipital lobes during MI of usual gait compared to controls.
Agosta, 2017*	fMRI	25 FOG 19 Con	AOT: 69.0 (8.0); Landscape: 64.0 (7.0) 66.0 (8.0)	10/2 8/5 9/10	OFF	-Foot tapping at 0.5 Hz -MI of FOG-provoking gait situations -AO of the same FOG-provoking situations	Whole brain	**AO training* vs. *landscape control intervention study. Only peak coordinates of group comparisons reported.* At baseline, PD and controls activated SMA, M1, frontal and parietal cortices and cerebellum across the tasks. During foot tapping, PD showed increased activations in lingual gyrus and right cerebellum crus I. During MI, FOG showed reduced activations across SMA and motor cortices and during AO also in bilateral caudate, left putamen and rolandic operculum as compared to controls.
Gilat, 2017 (#)	fMRI	23 PD 12 Con	65.0 (7.2) 65.4 (6.9)	18/5 6/6	OFF & ON	Foot tapping + VR of a straight corridor vs. passive watching of the VR screen	Whole brain + ROI	PD recruited M1 both in OFF and ON. In ON, PD also recruited pre-SMA, visual cortex and cerebellum, while in OFF PD recruited bilateral orbitofrontal cortices. In ON, step time variability was associated with increased activation across the bilateral cerebellar hemispheres, while in OFF step time variability was associated with

Table 1 (continued)

Study	Imaging technique	Sample	Age in years mean (SD)	Sex M/F	Med status	Task of interest	Analysis type	Key findings
								reduced activation across the dorsal premotor and posterior parietal cortices.
Maidan, 2017*	fMRI	34 PD	TT: 71.5 (1.5) TT + VR 71.2 (1.7)	12/5 11/6	ON	MI of gait with usual and obstacle pathway conditions presented as pictures on screen	Whole brain	**Treadmill (TT)* vs. *Treadmill plus VR (TT + VR) intervention study. Only outcomes of the intervention (no baseline) reported.* TT + VR showed lower activation in the anterior prefrontal cortex and right inferior frontal gyrus post intervention compared to TT, while TT had lower activation in the left lateral cerebellum and left middle temporal gyrus compared to TT + VR.
Nieuwhof, 2017 (#)	fMRI	19 PD 26 Con	70.7 (6.1) 71.2 (5.3)	15/4 16/10	ON	Foot tapping in fixed auditory cued rhythm with- or without cognitive dual task	Whole brain + ROI	During foot tapping, both PD and controls activated medial frontal and paracentral areas, including SMA and M1, as well as cerebellum and bilateral temporal gyri.
Ehgoetz Martens, 2018	fMRI	41 FOG	67.8 (6.4)	32/9	OFF	Foot tapping + VR with FOG- provoking task conditions.	ROI	Freezing events were associated with a loss of synchrony between the cortex and striatum and less segregation and specificity between cortical-striatal pathways.
Myers, 2018	fMRI	13 FOG 24 NF	65.1 (10.4) 65.8 (8.0)	10/3 13/11	OFF	MI of forward and backward gait vs. rest	ROI	Tango dance vs. Treadmill vs. Stretching intervention study. FOG showed decreased activations across primary sensory and motor cortical as well as cerebellar ROI's during MI of backward gait compared to NF.
Matar, 2019*	fMRI	19 FOG	65.3 (6.3)	16/3	OFF & ON	Foot tapping + VR of doorways	Whole brain + ROI	**Only effect of medication status (OFF* vs. *ON) reported.* Freezing-like delayed footsteps while passing a doorway in OFF were associated with decreased activation in the pre-SMA and left STN as compared to ON.

NOTE: Studies highlighted in italics were included in the exploratory ALE meta-analysis for PD, and studies marked with (#) were also included in the meta-analysis for healthy older adults. Instances when studies reporting whole brain coordinates could not be included in the meta-analyses are marked with an asterisk (*) and explained in *italic* font in the key findings column

PD Parkinson's disease, *Con* healthy older adults (i.e. controls), *YA* young adults, *FOG* PD patients with freezing of gait, *NF* PD patients without freezing of gait, *SPECT* single-photon emission computed tomography, *PET* positron emission tomography, *fMRI* task-based functional magnetic resonance imaging, *MI* motor imagery, *VI* visual imagery, *VR* virtual reality, *AO* action observation, *ROI* region of interest, *ICA* independent component analysis, *M1* primary motor cortex, *SMA* supplementary motor area, *CLR* cerebellar locomotor region, *MLR* mesencephalic locomotor region, *STN* subthalamic nucleus, *DBS* deep brain stimulation, *N.R.* not reported

Table 2 Overview of the experiments included in the exploratory ALE-meta analyses

Exp.	Study	Imaging technique	*N*	Mean (SD) age in years	Sex M/F	Med status	Sub-group	Task	Contrast	# Foci
Parkinson's disease (total 161 foci)										
1	Hanakawa, 1999a	SPECT	10	67.0 (4.2)	6/4	OFF	–	Actual walking on a treadmill	Actual gait > rest	16
2.1	Snijders, 2011	fMRI	12	58.7 (9.0)	8/4	OFF	FOG	MI gait	MI gait > VI	1
2.2	Snijders, 2011	fMRI	24	60.2 (8.9)	15/9	OFF	–	MI gait	MI gait > 'baseline rest' provided by inter-trial epochs	9
3	Crémers, 2012	fMRI	15	65.1 (9.5)	8/7	ON	–	MI gait	MI gait > MI standing	3
4.1	Gilat, 2015	fMRI	17	67.4 (6.2)	13/4	OFF	FOG	Foot tapping + VR	Straight walking in VR	15
4.2	Gilat, 2015	fMRI	17	67.4 (6.2)	13/4	OFF	FOG	Foot tapping + VR	Going through 90° turns in VR	8
4.3	Gilat, 2015	fMRI	10	64.8 (4.1)	9/1	OFF	NF	Foot tapping + VR	Straight walking in VR	10
4.4	Gilat, 2015	fMRI	10	64.8 (4.1)	9/1	OFF	NF	Foot tapping + VR	Going through 90° turns in VR	9
5.1	Tard, 2015	PET. ^{18}FDG	11	61.4 (4.8)	7/4	OFF	FOG	Actual walking a FOG provoking course	Actual gait > rest	17
5.2	Tard, 2015	PET. ^{18}FDG	11	62.2 (3.4)	8/3	OFF	NF	Actual walking a FOG provoking course	Actual gait > rest	14
6	Maillet, 2015	PET.H2^{15}O	8	63.3 (6.3)	4/4	OFF	–	MI gait	(MI-control) > (VI-control)	15
7	Weiss, 2015	PET.H2^{15}O	10	–	–	–	STN-DBS	MI gait	Main effect of MI gait > MI standing	2
8	Maidan, 2016	fMRI	20	72.9 (1.6)	14/6	ON	–	MI gait	MI obstacle gait > MI gait	10
9	Nieuwhof, 2017	fMRI	19	70.7 (6.1)	15/4	ON	–	Foot tapping + cues	Bilateral foot tapping on fixed auditory cued rhythm	15
10.1	Gilat, 2017	fMRI	23	65.0 (7.2)	18/5	OFF	–	Foot tapping + VR	Foot tapping in VR > passive watching VR	8
10.2	Gilat, 2017	fMRI	23	65.0 (7.2)	18/5	ON	–	Foot tapping + VR	Foot tapping in VR > passive watching VR	9
Healthy older adults (total 264 foci)										
1	Hanakawa, 1999a	SPECT	10	67.0 (4.0)	6/4	–	–	Actual gait on a treadmill	Actual gait > rest	18
2.1	La Fougere, 2010	PET. ^{18}FDG	16	61.3 (7.8)	9/7	–	–	Actual gait	Actual gait > rest	14
2.2	La Fougere, 2010	PET. ^{18}FDG	16	61.3 (7.8)	9/7	–	–	MI gait	MI gait > MI lying	20
3	Snijders, 2011	fMRI	21	57.0 (9.1)	12/9	–	–	MI gait	MI > 'baseline rest' provided by inter-trial epochs	20
4	Crémers, 2012	fMRI	15	63.8 (8.1)	7/8	–	–	MI gait	MI gait > MI standing	32
5	Zwergal, 2012	fMRI	20	Range: 60–78	N.R.	–	–	MI gait	MI gait > MI lying	14
6.1	Shimada, 2013	PET.^{18}FDG	12	77.4 (2.3)	0/12	–	–	Actual gait	Actual gait > rest in subjects with low step time variability	12
6.2	Shimada, 2013	PET.^{18}FDG	12	78.7 (2.2)	0/12	–	–	Actual gait	Actual gait > rest in subjects with high step time variability	10
7.1	Allali, 2014	fMRI	14	66.0 (3.5)	4/10	–	–	MI gait	MI gait > control task of visually inspecting a picture of the same footpath	17
7.2	Allali, 2014	fMRI	14	66.0 (3.5)	4/10	–	–	MI gait		9

Table 2 (continued)

Exp.	Study	Imaging technique	*N*	Mean (SD) age in years	Sex M/F	Med status	Sub-group	Task	Contrast	# Foci
8	Maillet, 2015	PET:H2^{15}O	8	62.9 (6.7)	4/4	–	–	MI gait	MI gait on a difficult cobblestone path > MI gait on a regular footpath (MI-control) > (VI-control)	20
9	Maidan, 2016	fMRI	20	69.7 (1.3)	10/10	–	–	MI gait	MI obstacle gait > MI gait	13
10	Nieuwhof, 2017	fMRI	26	71.2 (5.3)	16/10	–	–	Foot tapping + cues	Bilateral foot tapping on fixed auditory cued rhythm	21
11	Gilat, 2017	fMRI	12	65.4 (6.9)	6/6	–	–	Foot tapping + VR	Foot tapping in VR > passive watching VR	2
12.1	Sacheli, 2018	fMRI	22	66.7 (6.9)	13/9	–	–	MI gait	MI gait > MI standing	20
12.2	Sacheli, 2018	fMRI	22	66.7 (6.9)	13/9	–	–	MI gait + foot tapping in rhythm of MI gait	MI gait + foot tapping > MI standing + foot tapping	22

the most consistent activation was found in the CLR (194 voxels, peak voxel: − 2/− 52/− 8) and within the control group the most consistent activation was found in the midline SMA (181 voxels, peak voxel: 2/− 4/64) and leg area of M1 (94 voxels, peak voxel: 6/− 34/74). The same areas also survived the random effects ALE subtraction analysis (see Fig. 1c, d).

Methods Used to Study the Neural Control of Gait in PD

The pros and cons of the different neuroimaging methods used to study gait in the included studies have been extensively reviewed by others (e.g. see [1•, 20••, 25]). As expected, most studies resulting from our systematic search used either MI of gait or bilateral foot tapping during fMRI. One noteworthy recent development is that studies started to combine foot tapping paradigms with cognitive dual tasking to model the neural correlates underlying gait automaticity impairments in PD [29] and healthy elderly [7•]. Perhaps the most prominent feature of gait in PD is that it progressively fails to fall under automatic control, thus forcing patients to increasingly rely on compensatory circuits to control their steps [16]. The loss of motor automaticity is linked to the loss of dopaminergic innervation in the posterior striatum [43], but how exactly patients achieve compensatory stepping and the clinical impact of when these compensatory circuits fail remains largely unknown [16, 29]. Interestingly, Bürki et al. [7•] used two different cognitive tasks during foot tapping in the elderly, namely a verbal fluency task and a serial subtraction task inside as well as outside the scanner, the latter while walking on a GaitRite mat. This allowed them to investigate differential effects of distraction on foot tapping performance as well as on actual gait [7•]. Similar studies could be performed in PD that systematically increase the load on the attentional compensatory circuits that PD presumably rely on to perform otherwise automatic foot tapping. This would also help to map out the attentional compensatory circuits which are likely to converge across all task loads (i.e. both the cognitive and motor task). More studies using dual tasking combined with real gait and action simulation paradigms are needed to better map the failing automaticity and compensatory circuits that underpin gait in PD [29].

So far, only two studies by Hanakawa et al. [18, 19] used SPECT to assess the brain activations during actual treadmill gait in PD [18, 19]. Surprisingly, this methodology has never since been replicated by others, possibly due to increasing utility of PET over SPECT in medical imaging. A total of four studies utilized PET to compare the radiotracer uptake following a period of walking vs. rest. Two of these administered H2^{15}O [26, 41] and one ^{18}FDG isotopes [37] to study the general brain activation patterns resulting from neuronal oxygen and glucose consumption, respectively. One PET study used [^{11}C]-CFT to map changes in dopamine transporter

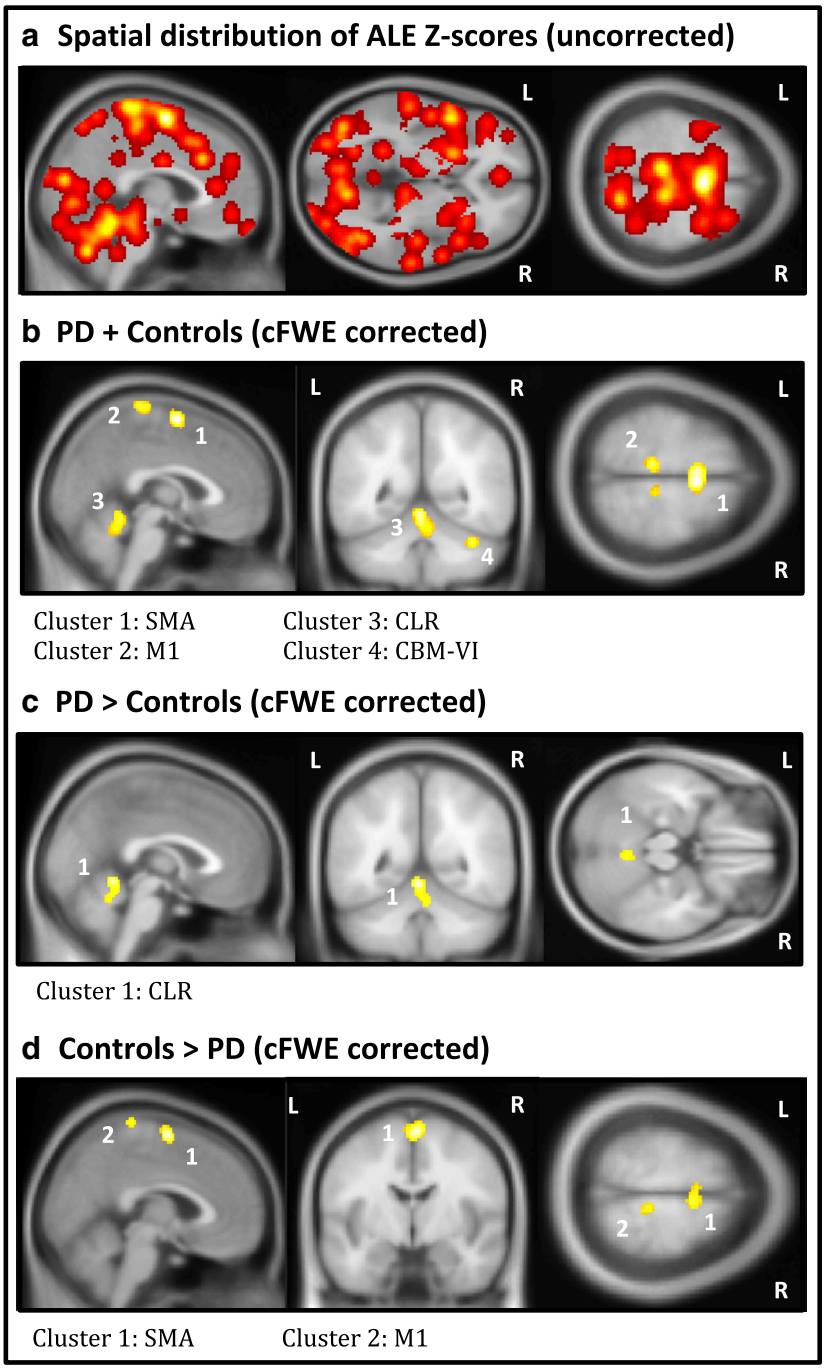

Fig. 1 Exploratory ALE meta-analysis results. **a** Spatial distribution of ALE z-scores across both PD and healthy older adults, uncorrected. **b** Significant gait-related activations found across both groups, cFWE corrected. **c** Significant CLR activations found in PD patients compared to healthy older adults, cFWE corrected. **d** Significant SMA and M1 activations found in healthy older adults as compared to PD patients, cFWE corrected. Abbreviations: ALE = activation of likelihood estimation; PD = Parkinson's disease; cFWE = cluster-wise family error corrected for multiple comparisons; L = left; R = right; SMA = supplementary motor area; M1 = primary motor cortex; CLR = cerebellar locomotor region; CBM-VI = lobule VI of the cerebellum

availability (DAT) in the striatum and extra-striatal regions following gait in PD [31].

Although the following studies did not make the inclusion criteria for the present review, their novel methodologies are worth a mention. Firstly, van der Hoorn et al. [39] used changes in optic flow to simulate a visual sensation of forward progression similar to that experienced during gait [39]. By suddenly changing the speed of the optic stimuli, a sensation of gait cessation could be induced. It can be envisioned that the combination of such changes in optic flow and foot tapping in a virtual environment could perhaps induce the sensation of near-falls to map the neural correlates of gait adaptation and fear of falling in PD and the elderly. Secondly, de Lima-Pardini et al. [9•] developed a unique apparatus with MRI-compatible force sensors that allowed for the simulation of anticipatory postural adjustments (APA) that are integral to the initiation of the first step [9•]. PD patients often show multiple APA's during gait initiation [22], and such novel methodologies hold strong potential to provide insights into these challenging gait epiphenomena.

Interpreting the Main Outcomes

One of the most consistent finding across studies was an altered involvement of the SMA during gait in PD. This is supported by our exploratory meta-analysis showing consistent SMA activation in healthy elderly controls, but not in PD. The SMA is part of the mesial premotor loop and highly connected to the putamen where it likely aids in the selection of appropriate motor sequences [28]. The lower SMA activation seen in PD may thus be the result of lower striatal activations following dopaminergic denervation. Structural white matter changes have also been shown in the SMA pathways [14]. Taken together, reduced SMA activation is likely a hallmark of impaired gait control in PD.

Another outcome that was supported by our exploratory meta-analysis was that gait in PD was consistently associated with increased activations across the cerebellum, and in particular the CLR. Interestingly, a recent study by Fasano et al. [13••] showed that the majority of brain lesions that result in freezing of gait are located in areas that have strong functional connections with the CLR in almost exactly the same peak location as seen in our exploratory analysis [13••]. Together, this indicates that PD patients are heavily reliant on the CLR to modulate their gait, perhaps due to the lack automatic control from the basal ganglia. In contrast, [43] found evidence based on PET-data that the cerebellum was involved in the pathophysiology of gait and balance problems in PD, as decreased levels of acetylcholinesterase were found in the midbrain and the cerebellum. Wu and Hallett [42] put forward a model in which both pathological and compensatory processes of the cerebellum could play a role in various symptoms of PD, including gait. This interplay of compensatory and pathological effects was projected to change with disease progression. The compensatory role of the cerebellum provides merit to develop interventions that attempt to modulate the cerebellar input during gait, such as split-belt training interventions [45]. Recently, excitatory theta burst stimulation applied to the cerebellar hemispheres induced gait speed improvements, although freezing of gait was not alleviated [46]. However, several studies on healthy older adults also found increased activations in the cerebellum, so the exact specificity of CLR activation to PD gait cannot be concluded from this exploratory meta-analysis. More data is required to support our preliminary findings and provide more insight into the complex role of the CLR.

Conclusions

Recent advances in neuroimaging allow for the investigation of the neural mechanisms underlying gait impairments in PD. Here, we show for the first time that different imaging methodologies complement each other and that their outcomes can be used to reveal the most consistent whole brain activations that are gait-related. This knowledge will aid in our focus to develop interventions, targeting the most prominent changes in the neural control of gait in PD. It is projected that with the inclusion of more future studies, such meta-analysis techniques will be able to reveal neural signatures that are specific to certain gait impairments in subtypes of PD.

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Compliance with Ethical Standards

Conflict of Interest Moran Gilat, Bauke W. Dijkstra, Nicholas D'Cruz, Alice Nieuwboer and Simon JG Lewis each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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