



**HAL**  
open science

## **Contribution of insula in Parkinson's disease: A quantitative meta-analysis study**

Marion Criaud, Leigh Christopher, Philippe Boulinguez, Bénédicte Ballanger,  
Anthony E. Lang, Sang S Cho, Sylvain Houle, Antonio P Strafella

### ► **To cite this version:**

Marion Criaud, Leigh Christopher, Philippe Boulinguez, Bénédicte Ballanger, Anthony E. Lang, et al.. Contribution of insula in Parkinson's disease: A quantitative meta-analysis study. *Human Brain Mapping*, 2017, 37, pp.1375 - 1392. <10.1002/hbm.23109>. <hal-05013711>

**HAL Id: hal-05013711**

**<https://hal.science/hal-05013711v1>**

Submitted on 31 Mar 2025

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



HAL Authorization

## Contribution of Insula in Parkinson's Disease: A Quantitative Meta-Analysis Study

Marion Criaud<sup>1,2,3,4,5,6</sup>, Leigh Christopher<sup>1,2,3</sup>, Philippe Boulinguez<sup>4,5,6</sup>, Benedicte Ballanger<sup>4,5,6</sup>, Anthony E. Lang<sup>1</sup>, Sang S. Cho<sup>1,2,3</sup>, Sylvain Houle<sup>2</sup>, and Antonio P. Strafella<sup>1,2,3,\*</sup>

<sup>1</sup>Morton and Gloria Shulman Movement Disorder Unit & E.J. Safra Parkinson Disease Program, Toronto Western Hospital, UHN, University of Toronto, Ontario, Canada

<sup>2</sup>Research Imaging Centre, Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, University of Toronto, Toronto, Ontario, Canada

<sup>3</sup>Division of Brain, Imaging and Behaviour – Systems Neuroscience, Krembil Research Institute, UHN, University of Toronto, Ontario, Canada

<sup>4</sup>Université Lyon 1, Villeurbanne, France

<sup>5</sup>Centre De Neurosciences Cognitive, CNRS, UMR5229, Bron, France

<sup>6</sup>Université De Lyon, Lyon, F-69622, France

### Abstract

The insula region is known to be an integrating hub interacting with multiple brain networks involved in cognitive, affective, sensory, and autonomic processes. There is growing evidence suggesting that this region may have an important role in Parkinson's disease (PD). Thus, to investigate the functional organization of the insular cortex and its potential role in parkinsonian features, we used a coordinate-based quantitative meta-analysis approach, the activation likelihood estimation. A total of 132 insular foci were selected from 96 published experiments comprising the five functional categories: cognition, affective/behavioral symptoms, bodily awareness/autonomic function, sensorimotor function, and nonspecific resting functional changes associated with the disease. We found a significant convergence of activation maxima related to PD in different insular regions including anterior and posterior regions bilaterally. This study provides evidence of an important functional distribution of different domains within the insular cortex in PD, particularly in relation to nonmotor aspects, with an influence of medication effect.

### Keywords

Parkinson's disease; insula; nonmotor symptoms; dopamine; cognition; behavior

---

\*Correspondence to: Antonio P. Strafella, MD, PhD, FRCPC; Toronto Western Hospital and Institute, UHN & Research Imaging Centre, CAMH, University of Toronto, Toronto, Ontario, Canada. antonio.strafella@uhn.ca and antonio.strafella@camhpet.ca.

## INTRODUCTION

In the past few years, the insula region has generated a great deal of interest, and while generally considered a limbic region, it is now known to be involved in numerous other functions. In fact, the insula is considered to be an integrating hub linking several functional systems, each comprised a set of anatomically and functionally different regions involved in cognitive, affective, sensory, and autonomic processes [Christopher et al., 2014a; Kurth et al., 2010]. This triangle-shaped area located in between the frontal, parietal, and temporal lobes is divided into four functional integrative nodes [Kurth et al., 2010]. The mid-posterior insula is implicated in somatomotor functions while the central insula participates in olfactory and gustatory tasks. The ventral anterior insula is linked to social and emotional functions, whereas the dorsal anterior insula is mainly involved in cognition.

To date, no studies have directly investigated the contribution of the insula to symptoms of PD. While PD is primarily considered a movement disorder, these patients are also afflicted by a large number of nonmotor symptoms, i.e., behavioral, cognitive, sensory, and autonomic disturbances [Chaudhuri and Schapira, 2009; Park and Stacy, 2009]. In general, imaging and neurophysiological studies investigating brain abnormalities in PD have focused on different cortical and subcortical regions but have never addressed the role of the insula, despite substantial evidence supporting its potential contribution to nonmotor symptoms in PD. While deposition of alpha-synuclein in the insula [Braak et al., 2006] can directly impair receptor function and synaptic activity in this region, the degeneration of dopaminergic, cholinergic, and serotonergic projecting neurons to the insula [Halliday et al., 1990] may also significantly disrupt its functional integrity. The subsequent loss of neurotransmitter modulation in the insula could affect information processing through heavy interconnections between the insula and different cortical regions (i.e., frontal, temporal, parietal, cingulate cortex) [Cauda et al., 2011; Nieuwenhuys, 2012] as well the basal ganglia [Chikama et al., 1997].

In a recent review, we highlighted the possible role of the insula in nonmotor symptoms of PD [Christopher et al., 2014a]. However, in order to investigate the functional organization of the insular cortex and its potential role in parkinsonian features, we applied a quantitative meta-analysis method to published neuroimaging studies to identify those core abnormalities consistently manifested across patient cohorts and range of tasks which are associated with the insula. We used a coordinate-based quantitative meta-analysis approach, the activation likelihood estimation (ALE) [Eickhoff et al., 2009; Wager et al., 2009] to overcome the classical limitations of neuroimaging studies such as heterogeneity of patient population and small sample sizes. This approach has been used consistently and successfully in a number of recent studies [Arsalidou et al., 2013; Criaud and Boulinguez, 2013; Herz et al., 2014; Kurth et al., 2010; Mutschler et al., 2009; Pan et al., 2012; Shao et al., 2014; Uddin et al., 2014].

## METHODS

### Literature Search

To review all imaging studies possibly involving the insula in Parkinson's disease, the Web of Science and Pubmed databases were examined from 1993 to 2015 using the following keyword combinations: "'Parkinson's disease' AND 'Insula'," "'Parkinson's disease' AND 'functional magnetic resonance (fMRI)," "'Parkinson's disease' AND 'positron emission tomography (PET)'." This search resulted in 96 studies (Table I). Only fMRI and PET (receptor ligands and H<sub>2</sub>O<sup>15</sup>) studies were considered. All articles were screened for eligibility with the following inclusion criteria:

- English articles including original data
- Idiopathic PD patients
- No comparison with other brain pathologies
- No pharmacological trials
- 3D coordinates reported in stereotactic space (MNI or Talairach)
- Level of significance reported ( $p$  value, cluster or voxel level, correction)

For each study included, the coordinates located in the insular cortex were collected.

### Meta-Analysis Based on Activation Likelihood Estimation

To assess the functional role of the insular cortex in parkinsonian features, all imaging studies included in the meta-analysis were sorted into five functional categories. A total of 132 insular foci were selected from 96 published experiments (Table I, appendix) comprising the five functional categories: cognition (30 studies), affective/behavioral symptoms (24 studies), bodily awareness/autonomic function (8 studies), sensorimotor function (21 studies), and nonspecific resting functional changes associated with disease (13 studies). All Talairach coordinates were converted to MNI space using the Lancaster transform [Lancaster et al., 2007].

The ALE is a coordinate-based meta-analysis method. Activation maxima reported in studies (i.e., foci) are modeled as spatial 3D Gaussian probability distributions [Laird et al., 2005]. The distribution is centered at the reported coordinates and its size is directly related to the sample size (number of participants) [Eickhoff et al., 2009]. Once all the distributions of a study have been generated, a modeled activation map is created for the study [Turkeltaub et al., 2012]. The union of the modeled activation maps describing the convergence of results across studies at each voxel represents the ALE map. To identify true congruence from noise, permutation tests were performed. The ALE map was compared to the null distribution, a randomly distributed map, and tested for significance for each voxel [Eickhoff et al., 2012]. The meta-analysis was performed with Ginger ALE software (<http://brainmap.org/ale>). Statistical significance was set at a family-wise error corrected threshold of  $p < 0.05$  with a cluster extent of 10 voxels. The ALE value, cluster volume (in voxels), and the MNI coordinates are reported for each analysis. The maps of the ALE values were

superimposed on a colin.nii atlas [Laird et al., 2005] using the Mango software (<http://ric.uthscsa.edu/mango//mango.html>).

A meta-analysis was first conducted on all the imaging studies combined together to assess the contribution of all experiments to the insular activity results, and then separate meta-analyses were conducted on specific functional subcategories (cognition, sensorimotor, affective/behavioral symptoms) to evaluate the contribution of different experiments to the insular subregional findings. An analysis was also performed focusing only on blood flow studies (78: fMRI and H<sub>2</sub>O<sup>15</sup> PET, TC99m SPECT) representing the largest set of data in order to limit the possible confounding effect from metabolic (<sup>18</sup>F FDG) or receptor imaging and to test consistency of the results. When possible, a meta-analysis contrasting directly patients and controls (38 studies) was also performed and another set of analyses was conducted to estimate the effect of the medication on studies in which patients were evaluated ON and OFF medication.

## RESULTS

Table I (appendix) summarizes the demographics and experimental conditions of the 96 imaging reports included in the meta-analysis. Briefly, these included 20 PET studies with receptor imaging, 27 PET with H<sub>2</sub>O<sup>15</sup> or TC99m, and 51 fMRI. The total number of experiments (96) included 1852 patients (age 63 y/o  $\pm$  5 SD) and 801 controls (age 61 y/o  $\pm$  7 SD) (Table I, appendix). Thirty studies (31%) reported experiments related to cognition (executive function, memory, language, MCI, dementia, and so on), 24 studies (25%) reported experiments evaluative affective/behavioral symptoms, 8 studies (8%) were related to bodily awareness/autonomic function, 21 studies (22%) were associated with sensorimotor function, and 13 studies (14%) reported nonspecific changes associated with disease. In total, 30 studies evaluated the patients ON medications (562 patients), while 57 evaluated them OFF medication (830 patients).

The whole-group ALE meta-analysis across the 96 published experiments revealed significant convergence of activation maxima related to PD in different insular regions (Table II and Fig. 1). These clusters were located in the right ventral anterior insula ( $x=38, y=16, z=-2$ ; ALE value =0.050), left ventral anterior insula ( $x=-36, y=18, z=-8$ ; ALE value =0.039), left dorsal posterior insula ( $x=-42, y=-12, z=4$ ; ALE value =0.040), and right dorsal posterior insula ( $x=38, y=-16, z=4$ ; ALE value =0.039) (Fig. 1A).

When looking at those studies investigating only blood flow changes, there was an overlap with those clusters, in the right ventral anterior insula ( $x=36, y=16, z=0$ ; ALE value =0.042), the left ventral anterior insula ( $x=-38, y=18, z=-6$ ; ALE value =0.035), the right dorsal ( $x=38, y=-16, z=12$ ; ALE value =0.021), and the left dorsal insula ( $x=-40, y=-10, z=8$ ; ALE value =0.019) (Table III).

The ALE analysis performed on those studies comparing patients with healthy controls showed three significant clusters in similar regions, at the level of the right ventral anterior insula and the bilateral dorsal posterior insula ( $x=40, y=-16, z=2$ ; ALE value =0.022;  $x=-42, y=-12, z=4$ ; ALE value =0.024;  $x=36, y=18, z=-4$ ; ALE value =0.019).

When looking at the effect of the medication, a significant convergence of activation maxima was observed for the different medication states (ON or OFF) (Fig. 1B). The ON medication studies (30 experiments) showed a significant convergence of activation maxima in the left and right ventral anterior insula ( $x=-38, y=18, z=-8$ ; ALE value =0.022;  $x=32, y=26, z=-4$ ; ALE value =0.019), whereas in the OFF medication studies (57 experiments), convergence was localized more posteriorly, in the left and right dorsal posterior insula ( $x=-42, y=-12, z=4$ ; ALE value =0.036;  $x=38, y=-16, z=4$ ; ALE value =0.037).

A significant convergence of activation maxima was also observed for the different functional subcategories (Table IV). In fact, combining cognitive and behavioral/affective domains (54 studies) showed a significant convergence of activation maxima in the left and right ventral anterior insula ( $x=-34, y=20, z=-8$ ; ALE value =0.030;  $x=38, y=14, z=-4$ ; ALE value =0.027) and in the left and right dorsal posterior insula ( $x=-42, y=-12, z=4$ ; ALE value =0.039;  $x=38, y=-16, z=4$ ; ALE value =0.037) (Fig. 2A). In contrast, the analysis limited only to the cognitive domain identified smaller overlapping clusters (Fig. 3A) in the left and right ventral anterior insula ( $x=-36, y=20, z=-8$ ; ALE value =0.025;  $x=38, y=12, z=-4$ ; ALE value =0.022) and in the left and right dorsal posterior insula ( $x=-42, y=-12, z=2$ ; ALE value =0.030;  $x=36, y=-18, z=6$ ; ALE value =0.025). The behavioral/affective symptoms also showed an overlapping cluster in the right ventral mid-insula ( $x=44, y=2, z=-4$ ; ALE value =0.018) (Fig. 3B). When focusing on the effect of the dopaminergic medication on the behavioral/affective symptoms combined with cognition, a significant convergence of activation maxima was observed for the different medication stage (ON or OFF). The ON medication studies (21 experiments) showed a significant convergence of activation maxima in the left and right ventral anterior insula ( $x=-36, y=18, z=-8$ ; ALE value =0.019;  $x=32, y=26, z=-4$ ; ALE value =0.019), whereas in the OFF medication studies (28 experiments), convergence was localized more posteriorly, in the left and right dorsal posterior insula ( $x=-42, y=-12, z=4$ ; ALE value =0.035;  $x=38, y=-16, z=4$ ; ALE value =0.035) (Fig. 2B).

A significant convergence of activation maxima related to the sensorimotor function (21 studies) was seen instead in the left mid-insula ( $x=-42, y=6, z=-8$ ; ALE value =0.018) and the right anterior insula ( $x=44, y=18, z=-2$ ; ALE value =0.014), which did not overlap with other domain-related clusters (Table IV).

## DISCUSSION

Surprisingly, no neuroimaging studies have directly addressed the contribution of the insula as a critical region in PD pathology. This study confirmed the importance of the insula in PD in acting as a hub for processing critical information related to the body state and for integrating cognitive–affective, sensorimotor, and autonomic information (Fig. 1). This report provides evidence of an important functional distribution of different domains within the insular cortex in PD, particularly in relation to nonmotor aspects, with changes related to the effect of disease and medication state.

When focusing on the cognitive and behavioral/affective domains of the disease, the insula show a bilateral involvement of both anterior and posterior regions (Figs. 2 and 3). The

anterior involvement is quite consistent with accumulating research in healthy subjects showing that this region plays a central role in directing cognitive processes and implementing/maintaining task set [Dosenbach et al., 2006, 2007]. In conjunction with the anterior cingulate cortex (i.e., salience network), the anterior insula allows switching between neural networks required for executive functions [Menon and Uddin, 2010; Seeley et al., 2007; Swick et al., 2011]. It also has a well-established contribution to processing affect and emotion and it is critically involved in social interactions requiring self-awareness, interoception, and integration of both affective/emotional and environmental stimuli [Craig, 2009]. In other words, it is very likely that neurodegenerative processes affecting this region could disrupt both cognitive and socio/affective functions in PD [Christopher et al., 2014a; Nieuwenhuys, 2012].

An interesting finding was the observation in these PD patients (performing cognitive and behavioral/affective tasks) of a significant convergence of activation maxima in the posterior regions of the insula (Fig. 2B). While the biological explanation of this finding is not entirely clear, this may be the result of the dopaminergic changes described previously [Christopher et al., 2014b]. Indeed, when focusing on the effect of medication, we found some evidence supporting the role of dopamine depletion: PD patients OFF medication presented with a significant convergence of activation maxima mainly in dorsal posterior regions of the insula, while PD patients ON medication showed, in contrast, a more physiological involvement of bilateral anterior insula (Fig. 2B).

In patients studied OFF medication, the bodily sensations generated by the motor symptoms (i.e., bradykinesia and rigidity), it is possible that led to an abnormal activation of the posterior insula, an area generally implicated in the processing of position, movement, and sensation of the body [Chang et al., 2013; Cerasa et al., 2006]. This abnormal interoceptive information of how the body “feels” could lead to an abnormal salience processing in the anterior insula affecting how affective/emotional sensations are perceived in patients with PD, which is partially restored by dopaminergic medication. Alternatively, the more posterior activation in the OFF medication state (during cognitive and behavioral/affective tasks) may simply be related to a compensatory activation [Daselaar et al., 2015] due to inadequate recruitment of the anterior insula.

In contrast, when ON dopaminergic medication, patients might be better able to recruit the anterior insula during cognitive processing.

A significant convergence of activation maxima related specifically to sensorimotor tasks was seen in the mid-insula confirming the role of this region in processing bodily awareness in relation to somatosensory information and coordination of movement.

Although the ALE technique overcomes the classical limitations of neuroimaging studies, it only reveals convergences of activity from different studies, not the actual activations. To reduce potential confounding factors, we conducted as well a number of different analysis limited to only blood flow studies and comparing patients to healthy controls. In any case, interpretations of the results should be made taking into consideration the limitation inherent to this technique. Despite this, the technique offers a valuable approach to investigate an

under-recognized region involved in the pathogenesis of Parkinson's disease. The insula is substantially affected by alpha-synuclein deposition in PD and the insular abnormalities found in neuroimaging studies strongly point toward its contribution to a wide range of nonmotor symptoms, including somatosensory disturbances. Thus, as an important hub involved in integrating diverse information, the insula should be considered a region of interest when investigating cognitive and behavioral changes, as well as disruptions in viscerosensory or somatosensory processes in Parkinson's disease.

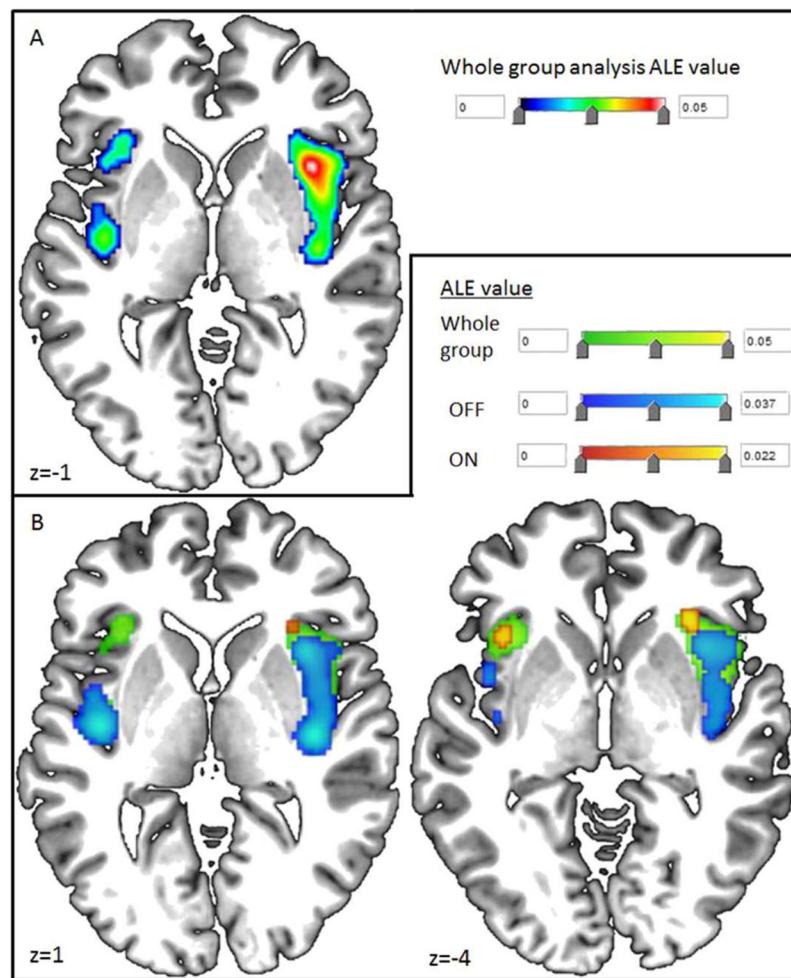
## Acknowledgments

Contract grant sponsor: Canadian Institutes of Health Research (MOP 136778); Contract grant sponsor: Canada Research Chair program

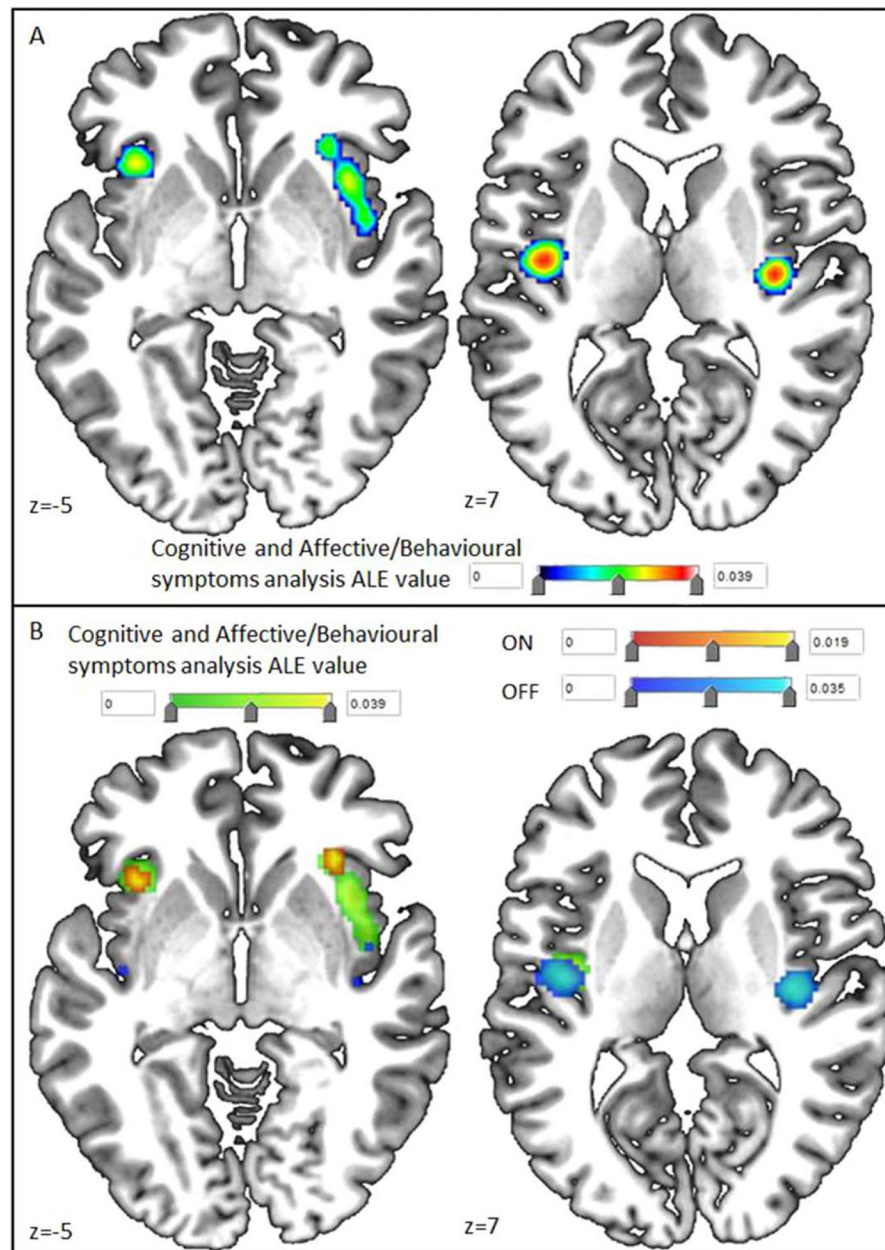
## References

- Arsalidou M, Duerden EG, Taylor MJ. The centre of the brain: Topographical model of motor, cognitive, affective, and somatosensory functions of the basal ganglia. *Hum Brain Mapp.* 2013; 34:3031–3054. [PubMed: 22711692]
- Braak H, Bohl JR, Muller CM, Rub U, de Vos RA, Del Tredici K. Stanley Fahn Lecture 2005: The staging procedure for the inclusion body pathology associated with sporadic Parkinson's disease reconsidered. *Movement Disord.* 2006; 21:2042–2051. [PubMed: 17078043]
- Cauda F, D'Agata F, Sacco K, Duca S, Geminiani G, Vercelli A. Functional connectivity of the insula in the resting brain. *Neuroimage.* 2011; 55:8–23. [PubMed: 21111053]
- Cerasa A, Hagberg GE, Peppe A, Bianciardi M, Gioia MC, Costa A, Castriota-Scanderbeg A, Caltagirone C, Sabatini U. Functional changes in the activity of cerebellum and frontostriatal regions during externally and internally timed movement in Parkinson's disease. *Brain Res Bull.* 2006; 71:259–269. [PubMed: 17113955]
- Chang LJ, Yarkoni T, Khaw MW, Sanfey AG. Decoding the role of the insula in human cognition: Functional parcellation and large-scale reverse inference. *Cereb Cortex.* 2013; 23:739–749. [PubMed: 22437053]
- Chaudhuri KR, Schapira AH. Non-motor symptoms of Parkinson's disease: Dopaminergic pathophysiology and treatment. *Lancet Neurol.* 2009; 8:464–474. [PubMed: 19375664]
- Chikama M, McFarland NR, Amaral DG, Haber SN. Insular cortical projections to functional regions of the striatum correlate with cortical cytoarchitectonic organization in the primate. *J Neurosci.* 1997; 17:9686–9705. [PubMed: 9391023]
- Christopher L, Koshimori Y, Lang AE, Criaud M, Strafella AP. Uncovering the role of the insula in non-motor symptoms of Parkinson's disease. *Brain.* 2014a; 137:2143–2143. [PubMed: 24736308]
- Christopher L, Marras C, Duff-Canning S, Koshimori Y, Chen R, Boileau I, Segura B, Monchi O, Lang AE, Rusjan P, Houle S, Strafella AP. Combined insular and striatal dopamine dysfunction are associated with executive deficits in Parkinson's disease with mild cognitive impairment. *Brain.* 2014b; 137:565–575. [PubMed: 24334314]
- Craig AD. How do you feel—now? The anterior insula and human awareness. *Nat Rev Neurosci.* 2009; 10:59–70. [PubMed: 19096369]
- Criaud M, Boulinguez P. Have we been asking the right questions when assessing response inhibition in go/no-go tasks with fMRI? A meta-analysis and critical review. *Neurosci Biobehav Rev.* 2013; 37:11–23. [PubMed: 23164813]
- Daselaar SM, Iyengar V, Davis SW, Eklund K, Hayes SM, Cabeza RE. Less wiring, more firing: Low-performing older adults compensate for impaired white matter with greater neural activity. *Cereb Cortex.* 2015; 25:983–990. [PubMed: 24152545]
- Dosenbach NU, Visscher KM, Palmer ED, Miezin FM, Wenger KK, Kang HC, Burgund ED, Grimes AL, Schlaggar BL, Petersen SE. A core system for the implementation of task sets. *Neuron.* 2006; 50:799–812. [PubMed: 16731517]

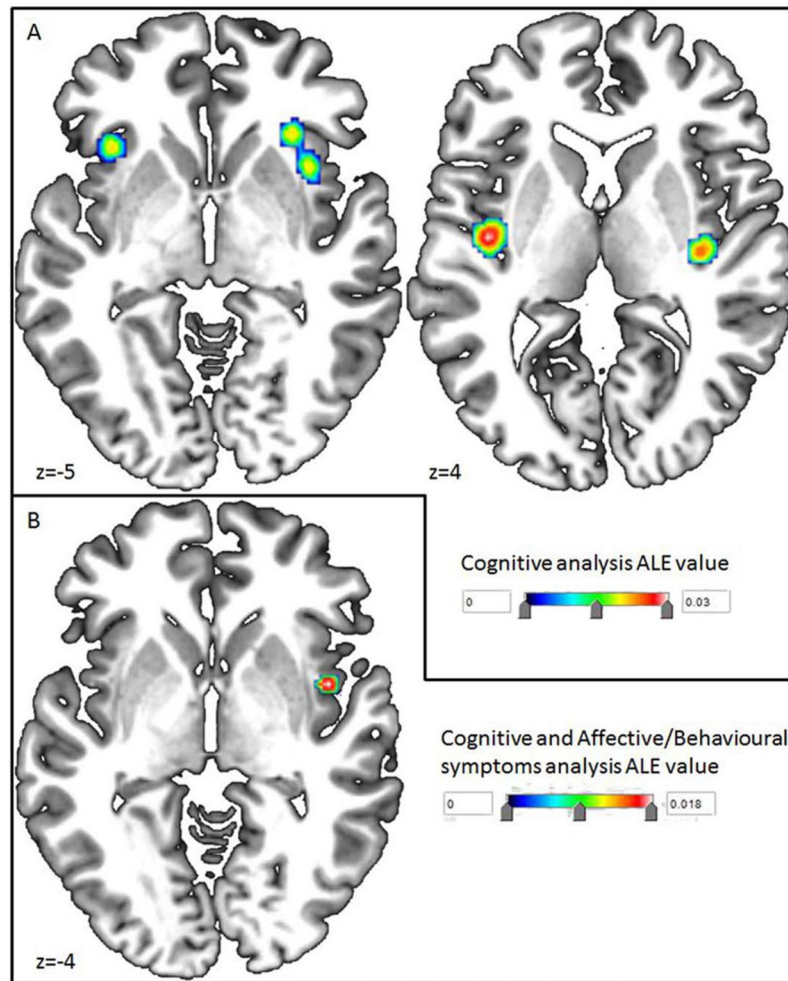
- Dosenbach NU, Fair DA, Miezin FM, Cohen AL, Wenger KK, Dosenbach RA, Fox MD, Snyder AZ, Vincent JL, Raichle ME, Schlaggar BL, Petersen SE. Distinct brain networks for adaptive and stable task control in humans. *Proc Natl Acad Sci USA*. 2007; 104:11073–11078. [PubMed: 17576922]
- Eickhoff SB, Laird AR, Grefkes C, Wang LE, Zilles K, Fox PT. Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: A random-effects approach based on empirical estimates of spatial uncertainty. *Hum Brain Mapp*. 2009; 30:2907–2926. [PubMed: 19172646]
- Eickhoff SB, Bzdok D, Laird AR, Kurth F, Fox PT. Activation likelihood estimation revisited. *Neuroimage*. 2012; 59:2349–2361. [PubMed: 21963913]
- Halliday GM, Li YW, Blumbergs PC, Joh TH, Cotton RG, Howe PR, Blessing WW, Geffen LB. Neuropathology of immunohistochemically identified brainstem neurons in Parkinson's disease. *Ann Neurol*. 1990; 27:373–385. [PubMed: 1972319]
- Herz DM, Eickhoff SB, Løkkegaard A, Siebner HR. Functional neuroimaging of motor control in parkinson's disease: A meta-analysis. *Hum Brain Mapp*. 2014; 35:3227–3237. [PubMed: 24123553]
- Kurth F, Zilles K, Fox PT, Laird AR, Eickhoff SB. A link between the systems: Functional differentiation and integration within the human insula revealed by meta-analysis. *Brain Struct Funct*. 2010; 214:519–534. [PubMed: 20512376]
- Laird AR, Fox M, Price CJ, Glahn DC, Uecker AM, Lancaster JL, Turkeltaub PE, Kochunov P, Fox PT. ALE meta-analysis: Controlling the false discovery rate and performing statistical contrasts. *Hum Brain Mapp*. 2005; 25:155–164. [PubMed: 15846811]
- Lancaster JL, Tordesillas-Gutierrez D, Martinez M, Salinas F, Evans A, Zilles K, Mazziotta JC, Fox PT. Bias between MNI and Talairach coordinates analyzed using the ICBM-152 brain template. *Hum Brain Mapp*. 2007; 28:1194–1205. [PubMed: 17266101]
- Menon V, Uddin LQ. Saliency, switching, attention and control: A network model of insula function. *Brain Struct Funct*. 2010; 214:655–667. [PubMed: 20512370]
- Mutschler I, Wieckhorst B, Kowalevski S, Derix J, Wentlandt J, Schulze-Bonhage A, Ball T. Functional organization of the human anterior insular cortex. *Neurosci Lett*. 2009; 457:66–70. [PubMed: 19429164]
- Nieuwenhuys R. The insular cortex: A review. *Progr Brain Res*. 2012; 195:123–163.
- Pan PL, Song W, Shang HF. Voxel-wise meta-analysis of gray matter abnormalities in idiopathic Parkinson's disease. *Eur J Neurol*. 2012; 19:199–206. [PubMed: 21762435]
- Park A, Stacy M. Non-motor symptoms in Parkinson's disease. *J Neurol*. 2009; 256:293–298. [PubMed: 19711119]
- Shao N, Yang J, Li J, Shang HF. Voxelwise meta-analysis of gray matter anomalies in progressive supranuclear palsy and Parkinson's disease using anatomic likelihood estimation. *Front Hum Neurosci*. 2014; 8:63. [PubMed: 24600372]
- Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL, Greicius MD. Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci*. 2007; 27:2349–2356. [PubMed: 17329432]
- Swick D, Ashley V, Turken U. Are the neural correlates of stopping and not going identical? Quantitative meta-analysis of two response inhibition tasks. *Neuroimage*. 2011; 56:1655–1665. [PubMed: 21376819]
- Turkeltaub PE, Eickhoff SB, Laird AR, Fox M, Wiener M, Fox PT. Minimizing within-experiment and within-group effects in activation likelihood estimation meta-analyses. *Hum Brain Mapp*. 2012; 33:1–13. [PubMed: 21305667]
- Uddin LQ, Kinnison J, Pessoa L, Anderson ML. Beyond the tripartite cognition-emotion-interoception model of the human insular cortex. *J Cogn Neurosci*. 2014; 26:16–27. [PubMed: 23937691]
- Wager TD, Lindquist MA, Nichols TE, Kober H, Van Snellenberg JX. Evaluating the consistency and specificity of neuroimaging data using meta-analysis. *Neuroimage*. 2009; 45:S210–S221. [PubMed: 19063980]



**Figure 1.** ALE map of clusters showing changes in PD ( $p < 0.05$ ). (A) Whole group analysis. (B) Effect of the medication.



**Figure 2.** ALE map of clusters showing changes in PD ( $p < 0.05$ ). (A) Cognitive and affective/behavioral symptoms analysis. (B) Effect of the medication on cognitive and affective/behavioral symptoms.



**Figure 3.** ALE map of clusters showing changes in PD ( $p < 0.05$ ). (A) Cognitive analysis. (B) Affective/behavioral symptoms.

TABLE I

List of studies including first author, year of publication, the contrast used, and the medication state during the task, the subcategory, the number of patients and controls, the age of each group, the UPDRS, and the state of medication during the evaluation and the modality

First author	Year	Contrasts (ON/OFF)	Category	N PD (vs. N control group)	Age	UPDRS-III (ON/OFF)	Modality
Ballanger	2010	PD with visual hallucination vs. CPD (ON)	Affective & Behavioural symptoms (Visual Hallucination)	7 PD with visual hallucinations (7 CPD)	69 PD (67 CPD)	24 vs 15 (ON)	PET ( <sup>18</sup> F Setoperone)
<i>Rest</i>							
Ballanger	2012	PD vs NC (OFF)	Other	8 PD (7 NC)	63 PD	27 (OFF)	PET ( <sup>18</sup> F MPPF)
<i>Rest</i>							
Ballanger	2012	PD with depression vs NC (OFF)	Affective & Behavioural symptoms (Depression)	4 PD with depression (7 NC)	54 PD with depression	26 (OFF)	PET ( <sup>18</sup> F MPPF)
<i>Rest</i>							
Ballanger	2012	PD with depression vs CPD (OFF)	Affective & Behavioural symptoms (Depression)	4 PD with depression (8 CPD)	54 with depression	26 (OFF)	PET ( <sup>18</sup> F MPPF)
<i>Rest</i>							
Beyer	2008	PD with early dementia vs PD with late dementia (ON)	Cognition (Dementia)	9 PD with early dementia (6 PD with late dementia)	74 PD with early dementia (70 PD with late dementia)	40 vs 40 (ON)	fMRI
<i>Rest</i>							
Bohlhalter	2009	Correlation between somatosensory discrimination and working memory scale (OFF)	Cognition (Working Memory and Somatosensory Discrimination)	12 PD (12 NC)	59 PD (47 NC)	17 (ON)	PET (H <sup>15</sup> O)
<i>Task: somatosensory discrimination</i>							
Borghammer	2012	PD vs NC (OFF)	Other	21 PD (11 NC)	64 PD (60 NC)	16 (ON)	PET ( <sup>18</sup> F FDG)
<i>Rest</i>							
Brefel-Courbon	2005	Pain induced activity, PD vs NC (OFF)	Bodily Awareness (Pain)	9 PD (9 NC)	65 PD	25 (OFF)	PET (H <sup>15</sup> O)
<i>Task: cold water stimulation inducing painful or nonpainful sensation on the hand</i>							
Brefel-Courbon	2005	Pain induced activity, PD vs NC (ON)	Bodily Awareness (Pain)	9 PD (9 NC)	65 PD	15 (ON)	PET (H <sup>15</sup> O)
<i>Task: cold water stimulation inducing painful or non-painful sensation on the hand</i>							
Brefel-Courbon	2005	Pain induced activity, PD OFF vs PD ON	Bodily Awareness (Pain)	9 PD	65 PD	25 OFF vs 15 ON	PET (H <sup>15</sup> O)
<i>Task: cold water stimulation inducing painful or non-painful sensation on the hand</i>							

First author	Year	Contrasts (ON/OFF)	Category	N PD (vs. N control group)	Age	UPDRS-III (ON/OFF)	Modality
Brefel-Courbon	2013	Pain-induced activity, CPD vs. PD with neuropathic pain (OFF)	Bodily awareness (pain)	9 PD with neuropathic pain (9CPD)	61 PD with neuropathic pain (65 CPD)	28 vs 25 (OFF)	PET ( <sup>18</sup> F)FDG
<i>Task: cold water stimulation inducing painful or non-painful sensation on the hand</i>							
Caproni	2013	1 finger sequence, PD vs NC (OFF)	Motor	11 PD (11 NC)	65 PD (65 NC)	20 (OFF)	fMRI
<i>Task: finger tapping sequences executed with the right hand, conditions: 1 finger sequence, simple 5 fingers sequences, complex 5 fingers sequence.</i>							
Caproni	2013	Simple 5 fingers sequence, PD vs NC (OFF)	Motor	11 PD (11 NC)	65 PD (65 NC)	20 (OFF)	fMRI
<i>Task: finger tapping sequences executed with the right hand, conditions: 1 finger sequence, simple 5 fingers sequences, complex 5 fingers sequence.</i>							
Caproni	2013	Complex 5 fingers sequence, NC vs PD (OFF)	Motor	11 PD (11 NC)	65 PD (65 NC)	20 (OFF)	fMRI
<i>Task: finger tapping sequences executed with the right hand, conditions: 1 finger sequence, simple 5 fingers sequences, complex 5 fingers sequence.</i>							
Cerasa	2006	Synchronized tapping vs rest, PD vs NC (OFF)	Motor	10 PD (11 NC)	64 PD (63 NC)	28 (OFF)	fMRI
<i>Task: Synchronized tapping with right index</i>							
Ceravolo	2011	PD PPTg stimulation ON vs OFF (OFF)	Other	6 PD	65 PD	74 PPTg ON vs 38 PPTg OFF (OFF)	PET ( <sup>18</sup> F)FDG
<i>Rest</i>							
Christopher	2013	NC vs PD with MCI (OFF)	Cognition (MCI)	11 PD with MCI (14 NC)	71 PD with MCI (68 NC)	31 (ON)	PET ( <sup>11</sup> C)FLB-457
<i>Rest</i>							
Christopher	2013	CPD vs PD with MCI (OFF)	Cognition (MCI)	11 PD with MCI (11 CPD)	71 PD with MCI (69 CPD)	31 vs 23 (ON)	PET ( <sup>11</sup> C)FLB-457
<i>Rest</i>							
Christopher	2014	NC vs PD with amnesic MCI (OFF)	Cognition (amnesic MCI)	9 PD with amnesic MCI (14 NC)	68 PD with amnesic MCI (68 NC)	36 (ON)	PET ( <sup>11</sup> C)FLB-457
<i>Rest</i>							
Christopher	2014	NC vs PD with MCI (OFF)	Cognition (MCI)	10 PD with MCI (14 NC)	70 PD with MCI (68 NC)	21 (ON)	PET ( <sup>11</sup> C)FLB-457
<i>Rest</i>							
Christopher	2014	CPD vs PD with amnesic MCI (OFF)	Cognition (amnesic MCI)	9 PD with amnesic MCI (11 CPD)	68 PD with amnesic MCI (69 CPD)	36 vs 23 (ON)	PET ( <sup>11</sup> C)FLB-457
<i>Rest</i>							
Christopher	2014	CPD vs PD with MCI (OFF)	Cognition (MCI)	10 PD with MCI (11 CPD)	70 PD with MCI (69 CPD)	21 vs 23 (ON)	PET ( <sup>11</sup> C)FLB-457

First author	Year	Contrasts (ON/OFF)	Category	N PD (vs. N control group)	Age	UPDRS-III (ON/OFF)	Modality
<i>Rest</i>							
Christopher	2014	PD with MCI vs PD with amnesic MCI (OFF)	Cognition (amnesic MCI)	9 PD with amnesic MCI (10 PD with MCI)	68 PD with amnesic MCI (70 PD with MCI)	36 vs 21 (ON)	PET ( <sup>11</sup> C-FLB457)
<i>Rest</i>							
Christopher	2014	Correlation between brain activity and memory score (OFF)	Cognition (amnesic MCI)	9 PD with amnesic MCI	68 PD with amnesic MCI	36 (ON)	PET ( <sup>11</sup> C-FLB457)
<i>Rest</i>							
Cilia	2008	Gambling PD vs CPD (OFF)	Affective & Behavioural symptoms (Gambling)	11 gambling PD (40 CPD)	57 gambling PD (55 CPD)	18 vs 19 (ON)	SPECT (TC99m)
<i>Rest</i>							
Cilia	2011	Correlation activity change and gambling score (OFF)	Affective & Behavioural symptoms (Gambling)	15 gambling PD	60 gambling PD	17 (ON)	SPECT (TC99m)
<i>Rest</i>							
Cools	2006	Error vs correct responses	Cognition (Learning)	14 PD	66 PD	39 OFF vs 16 ON	fMRI
<i>Task: probabilistic reversal learning task</i>							
Delaveau	2009	Placebo vs Levodopa during task recognition (OFF)	Affective & Behavioural symptoms (Emotion recognition)	14 PD	61 PD		fMRI
<i>Task: emotional face matching</i>							
Delaveau	2010	NC vs PD (OFF)	Affective & Behavioural symptoms (Emotion recognition)	14 PD (13 NC)	61 PD (56 NC)		fMRI
<i>Task: emotional face matching</i>							
Delaveau	2010	PD placebo vs L-dopa	Affective & Behavioural symptoms (Emotion recognition)	14 PD (13 NC)	61 PD (56 NC)		fMRI
<i>Task: emotional face matching</i>							
Dellapina	2012	Anti-correlation between brain activity and pain threshold (OFF)	Bodily Awareness (Pain)	8 PD with pain (8 CPD)	65 PD with pain (62 CPD)	16 vs 12 (OFF)	PET (H <sup>15</sup> O)
<i>Task: cold water stimulation inducing painful or non-painful sensation on the hand</i>							
Elsinger	2003	Synchronized tapping vs rest (OFF)	Motor	10 PD	67 PD	24 (OFF)	fMRI
<i>Task: Synchronized tapping with right index</i>							
Fregni	2006	NC vs PD with depression (OFF)	Affective & Behavioural symptoms (Depression)	26 PD with depression (29 NC)	66 PD with depression (65 NC)	35 (ON)	SPECT (TC99m)

First author	Year	Contrasts (ON/OFF)	Category	N PD (vs. N control group)	Age	UPDRS-III (ON/OFF)	Modality
<i>Rest</i>							
Gamma	2014	PD with visual hallucination vs PD with visual hallucination and cognitive dysfunction (ON)	Cognition (Cognitive Dysfunction in Visual Hallucinations)	6 PD with visual hallucination and cognitive dysfunction (5 PD with visual hallucination)	71 PD	23 (ON)	fMRI
<i>Rest</i>							
Goldman	2014	CPD vs PD with visual hallucination (ON)	Affective & Behavioural symptoms (Visual Hallucination)	25 PD with visual hallucination (25 CPD)	75 PD with visual hallucination (75 CPD)	44 vs 39 (ON)	fMRI
<i>Rest</i>							
Hanakawa	1999	Walk vs rest, PD vs NC (OFF)	Motor	10 PD (10 NC)	67 PD (67 NC)	35 (OFF)	SPECT (TC99m)
<i>Task: Walking or resting just before the scan</i>							
Helmich	2010	Connectivity from the anterior putamen, NC vs PD (OFF)	Other	41 PD (36 NC)	57 PD (57 NC)	28 (OFF)	fMRI
<i>Rest</i>							
Helmich	2010	Connectivity from the posterior putamen, PD vs NC (OFF)	Other	41 PD (36 NC)	57 PD (57 NC)	28 (OFF)	fMRI
<i>Rest</i>							
Hsu	2007	PD vs NC (OFF)	Other	27 PD (24 NC)	66 (62 NC)	26 (ON)	SPECT (TC99m)
<i>Rest</i>							
Hyoung	2010	CPD vs PD with MCI (OFF)	Cognition (MCI)	18 PD with MCI (20 CPD)	66 PD with MCI (62 CPD)	25 vs 22 (ON)	PET ( <sup>18</sup> F FDG)
<i>Rest</i>							
Imon	1999	PD Hoen and Yahr stage 3 or 4 vs NC (ON)	Other	12 PD Hoen and Yahr stage 3 or 4 (48 NC)	63 PD Hoen and Yahr stage 3 or 4 (58 NC)		SPECT (TC99m)
<i>Rest</i>							
Jech	2012	PD before vs after STN-DBS surgery (OFF)	Motor	12 PD	56 PD	34 vs 23 (OFF)	fMRI
<i>Task: Tapping with left or right hand</i>							
Kaasinen	2004	Anti-correlation novelty seeking scale and brain activity (OFF)	Cognition (Executive)	28 PD	62 PD	39 (ON)	PET ( <sup>11</sup> C FLB 457)
<i>Rest</i>							

First author	Year	Contrasts (ON/OFF)	Category	N PD (vs. N control group)	Age	UPDRS-III (ON/OFF)	Modality
Kahan	2012	Interaction movement and STN stimulation (ON/OFF), (OFF)	Motor	10 PD	58 PD	21 (OFF)	fMRI
<i>Task: voluntary hand movement</i>							
Kikuchi	2001	NC vs PD Hoen and Yahr stage 3/4 (ON)	Other	11 PD Hoen and Yahr stage 3 or 4 (11 NC)	59 PD Hoen and Yahr stage 3/4 (62 NC)	28 (ON)	SPECT (TC99m)
<i>Rest</i>							
Kikuchi	2001	PD Hoen and Yahr stage 1/2 vs PD Hoen and Yahr stage 3/4 (ON)	Other	11 PD Hoen and Yahr stage 3 or 4 (7 PD Hoen and Yahr stage 1 or 2)	59 PD Hoen and Yahr stage 3/4 (60 PD Hoen and Yahr stage 1/2)	19 vs 28 (ON)	SPECT (TC99m)
<i>Rest</i>							
Kostic	2010	PD vs NC (ON)	Other	24 PD (26 NC)	65 PD (63 NC)	19 (ON)	fMRI
<i>Rest</i>							
Kostic	2010	PD with depression vs CPD (ON)	Affective & Behavioural symptoms (Depression)	16 PD (24 CPD)	66 PD (65 CPD)	23 vs 19 (ON)	fMRI
<i>Rest</i>							
Lee	2014a	PD with MCI vs PD with MCI and dementia (ON)	Cognition (MCI and Dementia)	15 PD with MCI and dementia (36 PD with MCI)	73 PD with MCI and dementia (71 PD with MCI)	17 vs 20 (ON)	fMRI
<i>Rest</i>							
Lee	2014a	NC vs PD with MCI and dementia (ON)	Cognition (MCI and Dementia)	15 PD with MCI and dementia (25 NC)	73 PD with MCI and dementia (70 NC)	17 (ON)	fMRI
<i>Rest</i>							
Lee	2014b	PD with ICD vs CPD (OFF)	Affective & Behavioural symptoms (ICD)	11 PD with ICD (11 CPD)	57 PD with ICD (59 CPD)	14 vs 15 (ON)	PET ( <sup>18</sup> F-PP-CIT)
Lee	2014c	PD with high olfaction score vs NC (ON)	Autonomic symptoms (Olfaction)	38 PD with high olfaction score (50 NC)	69 PD with high olfaction score (69 NC)	18 (ON)	fMRI
<i>Rest</i>							
Liotti	2003	Phonation, before vs after voice therapy	Motor	5 PD with hypophonia	61 PD with hypophonia		PET (H <sup>15</sup> O)
<i>Task: speech task including phonation, reading and conversation</i>							
Loize	2009	Correlation with error in recognition (OFF)	Affective & Behavioural symptoms (Emotion recognition)	9 PD	66 PD	38 (OFF)	fMRI
<i>Task: emotional and non-emotional gesture recognition</i>							

First author	Year	Contrasts (ON/OFF)	Category	N PD (vs. N control group)	Age	UPDRS-III (ON/OFF)	Modality
Luo	2014	PD with depression vs NC (OFF)	Affective & Behavioural symptoms (Depression)	29 PD with depression (30 NC)	51 PD with depression (54 NC)	28 (OFF)	fMRI
<i>Rest</i>							
Maillet	2012	Hand movement, PD OFF vs PD ON	Motor	12 PD	60 PD	40 OFF vs 10 ON	fMRI
<i>Task: Hand movement and/or speech production</i>							
Mak	2014	PD with MCI vs CPD (ON)	Cognition (MCI)	24 PD with MCI (66 CPD)	69 PD with MCI (63 CPD)	20 vs 17 (ON)	fMRI
<i>Rest</i>							
Mallol	2007	NC vs PD (OFF)	Motor	13 PD (11 NC)	65 PD (62 NC)	23 (OFF)	fMRI
<i>Task: finger to thumb and hand rotation movements</i>							
Mattay	2002	PD OFF vs PD ON	Cognition (Working Memory)	10 PD	55 PD	9 OFF vs 5 ON	fMRI
<i>Task: N-back</i>							
Monchi	2004	Negative vs control feedback (OFF)	Cognition (Executive)	8 PD	57 PD	12 (OFF)	fMRI
<i>Task: Wisconsin Card Sorting Task with negative, positive and control feedback</i>							
Oishi	2004	Correlation verbal IQ score	Cognition (Executive)	44 PD	66 PD		SPECT (TC99m)
<i>Rest</i>							
Oishi	2004	Correlation full IQ score	Cognition (Executive)	44 PD	66 PD	(ON)	SPECT (TC99m)
<i>Rest</i>							
Pavese	2010	CPD vs PD with Fatigue (OFF)	Affective & Behavioural symptoms (Fatigue)	10 PD with fatigue (9 CPD)	65 PD with fatigue (63 CPD)	35 vs 33 (OFF)	PET ( <sup>18</sup> F-FDOPA)
<i>Rest</i>							
Pavese	2010	CPD vs PD with Fatigue (OFF)	Affective & Behavioural symptoms (Fatigue)	8 PD with fatigue (8 CPD)	65 PD with fatigue (64 CPD)	35 vs 34 (OFF)	PET ( <sup>11</sup> C-DASB)
<i>Rest</i>							
Payoux	2009	Interaction movement and GP stimulation (OFF)	Motor	5 PD	58 PD		PET (H <sup>15</sup> O)
<i>Task: Opening and clenching fist</i>							
Peran	2009	Generation of action verbs (ON)	Cognition (Language)	14 PD	64 PD		fMRI
<i>Task: object naming and generation of action verbs related to man-made or manipulable biological objects</i>							
Peran	2009	Generation of action verbs vs objects naming (man-man objects) (ON)	Cognition (Language)	14 PD	64 PD		fMRI

First author	Year	Contrasts (ON/OFF)	Category	N PD (vs. N control group)	Age	UPDRS-III (ON/OFF)	Modality
<i>Task: object naming and generation of action verbs related to man-made or manipulable biological objects</i>							
Peran	2009	Generation of action verbs with biological objects vs naming man-man objects (ON)	Cognition (Language)	14 PD	64 PD		fMRI
<i>Task: object naming and generation of action verbs related to man-made or manipulable biological objects</i>							
Peran	2009	Naming biological objects (ON)	Cognition (Language)	14 PD	64 PD		fMRI
<i>Task: object naming and generation of action verbs related to man-made or manipulable biological objects</i>							
Pinto	2004	Silent articulation, OFF STN DBS (OFF)	Motor	10 PD with STN DBS and dysarthria	54 PD with STN DBS and dysarthria	46 (OFF)	PET (H <sup>15</sup> O)
<i>Task: Speech, silent articulation or silence production</i>							
Pinto	2011	Hand movement, NC vs PD (OFF)	Motor	9 PD (15 NC)	59 PD (55 NC)	33 (ON)	fMRI
<i>Task: Hand movement and/or speech production</i>							
Pinto	2011	Hand movement and speech production NC vs PD (OFF)	Motor	9 PD (15 NC)	59 PD (55 NC)	33 (ON)	fMRI
<i>Task: Hand movement and/or speech production</i>							
Poisson	2013	PD with mirror movements vs CPD (OFF)	Motor	8 PD with mirror movements (6 CPD)	59 PD with mirror movements (65 CPD)	18 vs 16 (OFF)	fMRI
<i>Task: index to thumb opposition movement</i>							
Pollits	2013	Sexual vs neutral cue, PD with hypersexuality vs CPD (OFF)	Affective & Behavioural symptoms (Hypersexuality)	12 PD with hypersexuality (12 CPD)	55 PD with hypersexuality (62 CPD)	40 vs 35 (OFF)	fMRI
<i>Task: Rating the follow cues: dopaminergic drugs, appetizing food, money and gambling, sexual and neutral</i>							
Reijnders	2010	Anti-correlation apathy scale (ON)	Affective & Behavioural symptoms (Apathy)	55 PD	62 PD	17 (ON)	fMRI
<i>Rest</i>							
Robert	2012	Correlation apathy scale (ON)	Affective & Behavioural symptoms (Apathy)	45 PD	61 PD	8 (ON)	PET ( <sup>18</sup> F FDG)
<i>Rest</i>							
Rottschy	2013	Memory load, PD vs NC (ON)	Motor	23 PD (23 NC)	67 PD (65 NC)	24 (ON)	fMRI
<i>Task: memorize and retype variably long visuo-spatial stimulus sequences after short or long delays (immediate or delayed serial recall)</i>							
Sawamoto	2007	PD vs NC (OFF)	Cognition (Executive)	7 PD (9 NC)	59 PD (61 NC)	22 (OFF)	PET (H <sup>15</sup> O)
<i>Task: mental calculation of the day of the week depending on clues and instruction.</i>							

First author	Year	Contrasts (ON/OFF)	Category	N PD (vs. N control group)	Age	UPDRS-III (ON/OFF)	Modality
Schwingschuh	2013	Ankle movement, PD vs NC (ON)	Other	20 PD (10 NC)	67 PD (35 NC)	24 (ON)	fMRI
<i>Task: Cued ankle movement</i>							
Sheng	2014	PD with depression vs NC (ON)	Affective & Behavioural symptoms (Depression)	20 PD (25 NC)	56 PD (57 NC)		fMRI
<i>Rest</i>							
Sheng	2014	PD with depression vs CPD (ON)	Affective & Behavioural symptoms (Depression)	20 PD (21 CPD)	56 PD (57 CPD)		fMRI
<i>Rest</i>							
Shine	2013a	PD with visual hallucination vs CPD (ON)	Affective & Behavioural symptoms (Visual Hallucination)	9 PD (13 CPD)	66 PD (62 CPD)	27 vs 21 (ON)	fMRI
<i>Task: Bistable percept paradigm</i>							
Shine	2013a	PD with visual hallucination vs CPD (ON)	Affective & Behavioural symptoms (Visual Hallucination)	9 PD (13 CPD)	66 PD (62 CPD)	27 vs 21 (ON)	fMRI
<i>Rest</i>							
Shine	2013b	Complex vs simple cues, CPD vs PD with freezing gait (OFF)	Motor	14 PD with freezing gait (15 CPD)	63 PD with freezing gait (63 CPD)	32 vs 29 (OFF)	fMRI
<i>Task: Walk based stop signal task with simple or complex (Stoop based) cues.</i>							
Shine	2013c	Walk vs freezing (OFF)	Motor	18 PD	67 PD	39 (OFF)	fMRI
<i>Task: Walk based stop signal task with simple or complex (Stoop based) cues.</i>							
Song	2014	NC vs PD	Other	33 PD (33 NC)	71 PD (67 NC)	14	SPECT (TC99m)
<i>Rest</i>							
Subramanian	2011	Feedback vs no feedback group (ON)	Cognition (Executive)	10 PD	64 PD	15 (ON)	fMRI
<i>Task: Hand movement guided with or without neurofeedback</i>							
Tan	2015	NC vs PD (OFF)	Bodily Awareness (Pain)	14 PD (17 NC)	63 PD (61 NC)	22 (OFF)	fMRI
<i>Task: Heat-induced pain</i>							
Toxopeus	2012	Inhibition, NC vs PD (OFF)	Motor	13 PD (19 NC)	59 PD	22 (OFF)	fMRI
<i>Task: wrist movement divided in initiation, inhibition and gradual movement modulation.</i>							
Turner	2013	Movement-related activity, NC vs PD (OFF)	Motor	12 PD (12 NC)	57 PD (58 NC)	42 (OFF)	PET (H <sup>15</sup> O)
<i>Task: predictive visuomotor tracking task</i>							

First author	Year	Contrasts (ON/OFF)	Category	N PD (vs. N control group)	Age	UPDRS-III (ON/OFF)	Modality
Ulla	2010	Manic vs euthymic induced by STN DBS (ON)	Affective & Behavioural symptoms (Hypomania)	5 PD with hypomania	62 PD with hypomania	36 (OFF)	PET (H <sup>15</sup> O)
<i>Rest</i>							
Ventre-Dominey	2014	Spatial working memory, STN-DBS ON vs OFF (OFF)	Cognition (Working Memory)	13 PD	55 PD	9 DBS ON vs 39 DSB OFF (OFF)	PET (H <sup>15</sup> O)
<i>Task: spatial and non-spatial working color and movement association</i>							
Weder	2000	NC vs PD (OFF)	Cognition (Somatosensory discrimination)	12 NC		17 (ON)	PET (H <sup>15</sup> O)
<i>Task: finger exploratory discrimination</i>							
Welge-Lüssen	2009	Olfactory stimulation (ON)	Autonomic symptoms (Olfaction)	18 PD	59 PD	28 (ON)	fMRI
<i>Task: Olfactory stimulation</i>							
Wu	2011	PD vs NC (OFF)	Other	18 PD (18 NC)	62 PD (62 NC)	22 (OFF)	fMRI
<i>Rest</i>							
Ye	2012	PD vs NC (ON)	Cognition (Language)	16 PD (16 NC)	62 PD (64 NC)	16 (ON)	fMRI
<i>Task: Temporal connective comprehension</i>							

PD: Parkinson's disease patient, NC: normal control, CPD: control group of PD patients, MCI: mild cognitive impairment, STN: subthalamic nucleus, DBS: deep-brain stimulation, PPTg: nucleus tegmenti pedunculopontini, ON: ON medication (normal intake of medication), OFF: OFF medication (withdraw of medication over night).

**TABLE II**

Activation-likelihood-estimation: clusters from the whole group meta-analysis

Cluster	Side	k	ALE value	x	y	z
# 1	<b>R</b>	<b>477</b>	<b>0.050</b>	<b>38</b>	<b>16</b>	<b>-2</b>
	R		0.039	38	-16	4
# 2	<b>L</b>	<b>143</b>	<b>0.039</b>	<b>-36</b>	<b>18</b>	<b>-8</b>
	L		0.024	-32	24	4
# 3	L		0.021	-42	6	-8
	<b>L</b>	<b>119</b>	<b>0.040</b>	<b>-42</b>	<b>-12</b>	<b>4</b>

Location of significant convergence of activation maxima from the whole group meta-analysis, thresholded at  $p < 0.05$  (FWE-corrected), the side (R: right, L: left), the number of voxels (*k*), the ALE value, and the MNI coordinates.

TABLE III

Clusters from studies investigating the blood flow changes

Cluster	BA	Side	k	ALE value	x	y	z
# 1	48	R	337	0.042	36	16	0
		R		0.034	44	12	-6
# 2	48	L	136	0.035	-38	18	-6
	48	L		0.022	-34	24	6
	48	L		0.021	-42	8	-8
# 3	48	R	15	0.021	38	-16	12
# 4	48	L	12	0.019	-40	-10	8

Location of significant convergence of activation maxima from the whole group meta-analysis, thresholded at  $p < 0.05$  (FWE-corrected), the side (R: right, L: left), the number of voxels (*k*), the ALE value, and the MNI coordinates.

TABLE IV

Activation-likelihood-estimation from different functional subcategories

Cluster	Side	k	ALE value	x	y	z
<i>Cognition and affective/behavioral symptoms</i>						
# 1	R	115	0.027	38	14	-4
	R		0.024	42	4	-2
	R		0.022	32	26	-4
# 2	L	115	0.039	-42	-12	4
# 3	R	104	0.037	38	-16	4
# 4	L	54	0.030	-34	20	-8
<i>Cognition</i>						
# 1	L	85	0.030	-42	-12	2
# 2	R	62	0.025	36	-18	6
# 3	R	52	0.022	38	12	-4
	R		0.022	30	26	-4
# 4	L	37	0.025	-36	20	-8
<i>Affective/behavioral symptoms</i>						
# 1	R	15	0.018	44	2	-4
<i>Motor</i>						
# 1	L	32	0.018	-42	6	-8
# 2	R	11	0.014	44	18	-2

Location of significant convergence of activation maxima from the subcategory meta-analyses, thresholded at  $p < 0.05$  (FWE-corrected), the side (R: right, L: left), the number of voxels ( $k$ ), the ALE value, and the MNI coordinates.