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Action and emotion perception in Parkinson's disease: A neuroimaging *meta*-analysis

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ABSTRACT

Patients with Parkinson disease (PD) may show impairments in the social perception. Whether these deficits have been consistently reported, it remains to be clarified which brain alterations subtend them. To this aim, we conducted a neuroimaging *meta*-analysis to compare the brain activity during social perception in patients with PD versus healthy controls. Our results show that PD patients exhibit a significantly decreased response in the basal ganglia (putamen and pallidum) and a trend toward decreased activity in the mirror system, particularly in the left parietal cortex (inferior parietal lobule and intraparietal sulcus). This reduced activation may be tied to a disruption of cognitive resonance mechanisms and may thus constitute the basis of impaired others' representations underlying action and emotion perception. We also found increased activation in the posterior cerebellum in PD, although only in a within-group analysis and not in comparison with healthy controls. This cerebellar activation may reflect compensatory mechanisms, an aspect that deserves further investigation. We discuss the clinical implications of our findings for the development of novel social skill training programs for PD patients.

1. Introduction

Parkinson's disease (PD) is one of the most frequent neurodegenerative disorders (e.g., Marras et al., 2018). It is usually associated with manifest motor symptoms, such as tremor, bradykinesia and akinesia, but neurocognitive impairment and psychiatric disorders can also be observed (for recent reviews, see Aarsland et al., 2021; D'Iorio et al., 2021; Tolosa et al., 2021; Papagno and Trojano, 2018; Trojano and Papagno, 2018; Esposito et al., 2021). Within the neurocognitive sphere, PD can be characterized by disorders of social cognition (e.g., Gunnery et al., 2017; Pell et al., 2006; Sotgiu and Rusconi, 2013). Social perception is one of the main social abilities affected in patients with PD (Buxton et al., 2013), particularly for what concerns action observation (Agosta et al., 2017), face perception (Cardoso et al., 2010), and emotion recognition (Argaud et al., 2018). These social anomalies may lead to a wide range of negative outcomes, such as loneliness, stigma, and dehumanization, which might impair the patient's life more than other symptoms (Prenger et al., 2020). Despite this evidence, the neural substrates of social perception deficits in PD remain to be clarified (Bell et al., 2019).

PD is characterized by neurodegeneration of the basal ganglia, particularly the dopaminergic cells in the substantia nigra (Mallet et al., 2019). Although social deficits in PD have been related to dopamine depletion in these nuclei (Coundouris et al., 2019), particularly in the putamen (Palmeri et al., 2017), alterations in the functioning of other brain regions may contribute to the impairment. Among these, the cerebellum – which is known to be involved in cognitive processing beyond motor control (Hull, 2020; Schmahmann et al., 2019) - may play a critical role (Solstrand Dahlberg et al., 2020). Indeed, abnormal cerebellum activity has been observed in PD patients during both cognitive (e.g., Cao et al., 2011; Huang et al, 2007a; b) and social perception (e.g., Poisson et al., 2013) tasks, as well as during rest conditions (e.g., Zhan et al., 2018). Moreover, PD patients may show a hyper-metabolism in the cerebellum, possibly as a compensatory effort (Wu and Hallett, 2013): it is likely that the increased activity or connectivity in the cerebello-thalamo-cortical loop compensate the hypofunction in the striato-thalamo-cortical circuit to maintain function at a near normal level (Yu et al., 2007; Lewis et al., 2013). Indeed, the results of several studies suggest that the cerebellar hyperactivation allows patients with PD to execute motor tasks at the same level as healthy controls (e.g., Wu

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and Hallett, 2005). Moreover, machine-learning classification has shown that morphological alterations in the cerebellum are predictive of PD (Zeng et al., 2017). Importantly, however, the association between cerebellar activity and motor symptoms of PD is complex: in stark contrast to the compensatory mechanism hypothesis, changes in cerebellum activation have been associated with motor dysfunction of PD, such as resting tremor (Bostan and Strick, 2018), bradykinesia, and dyskinesias (Martinu and Monchi, 2013).

In addition to the basal ganglia and the cerebellum, other regions seem to be associated with social perception alterations in PD. Pohl et al. (2017) reported that emotion recognition in PD patients was associated with decreased responses in mirror neuron areas such as the inferior frontal gyrus (IFG), the inferior parietal lobule (IPL), and the supplementary motor cortex compared to healthy controls, possibly reflecting a disruption of neural resonance and thus be the basis of impaired emotion recognition in PD. In turn, other studies reported a somehow opposite pattern showing increased activation in somatosensory cortices (parietal lobe) during emotion recognition, this enhanced activation likely functioning as a compensatory mechanism for reduced striatal activation (Wabnegger et al., 2015). Furthermore, other studies reported a sub-cortical dysfunction during social perception processes in PD, particularly in the amygdala (Argaud et al., 2018). Neuroimaging results, however, have been overall inconsistent across studies (Bell et al., 2019).

Meta-analyses integrate experimental findings stemming from separate experiments into a unifying statistical model, thus highlighting the consistency of neural patterns shared by such experiments (Muller et al., 2018). Although a recent *meta*-analysis by Solstrand Dahlberg et al. (2020) addressed the neural mechanisms underlying cognitive and motor functions in PD, a neuroimaging *meta*-analysis for social processing in PD has not been carried out so far. Here, we implemented a coordinate-based *meta*-analysis on this topic, to clarify: (a) the neural bases of social perception processing in patients with PD and (b) the differences in social perception-related brain activation between patients with PD and healthy control (HC) participants. Specifically, we aimed to highlight the convergence across multiple experiments on social perception processes in patients with PD. Based on the literature, we expected to find in PD patients compared to healthy controls: a) a decreased activation in the frontal cortex and in the basal ganglia (see Pohl et al., 2017) and possibly b) evidence of increased activity in the cerebellum during processing of social information, which, as highlighted above, may be indicative of either beneficial compensatory mechanisms (Wu and Hallett, 2013), or motor dysfunction (Martinu and Monchi, 2013). Regarding effects in the parietal cortex, we do not have specific hypotheses, considering that opposite results have been reported (see Wabnegger et al., 2015 for compensatory mechanisms, and Pohl et al., 2017 for defective mechanisms).

2. Materials and methods

2.1. Rationale of the meta-analytic approach

We used a set of ALE *meta*-analyses to investigate the neural basis of impaired social perception in PD patients and their specificity with respect to healthy control individuals. Meta-analyses can overcome the limitations that individual neuroimaging experiments suffer from (Carp, 2012). To carry out the *meta*-analysis for this study, we resorted to ALE, a statistical approach that capitalizes on Montreal Neurological Institute (MNI) coordinates to integrate previously published experimental results (Turkeltaub et al., 2002). Using ALE, we carried out two different analyses: one on PD patients' data, and one on HC participants' data. After that, we contrasted the respective *meta*-analyses between the two groups. Our goal was to identify the group-specific brain activations underlying social perception, irrespective of experimental materials (i.e., verbal or pictorial stimuli) and employed tasks (e.g., implicit or explicit; action observation or evaluation tasks; etc.).

By taking into account the variety of experimental procedures (i.e. materials and tasks) that have been used in studies on social perception, and by aggregating such variety *meta*-analytically, we can more confidently ensure the generalizability of our results beyond specific methodological choices (Radua and Mataix-Cols, 2012). The criteria for including studies in our *meta*-analysis were defined by M.A., and then verified by the other authors. This multiple verification by independent investigators can minimize the selection bias (Muller et al., 2018).

2.2. Literature search and study selection

Our literature selection started by searching on Pubmed (https://www.ncbi.nlm.nih.gov/pubmed/) for the following keyword strings: "social cognition Parkinson *f*MRI", "social cognition Parkinson PET", "theory of mind Parkinson *f*MRI", "theory of mind Parkinson PET", "empathy Parkinson *f*MRI", "empathy Parkinson PET", "emotion Parkinson *f*MRI", "emotion Parkinson PET", "face Parkinson *f*MRI", "face Parkinson PET", "body Parkinson *f*MRI", "body Parkinson PET", "social perception Parkinson *f*MRI", "social perception Parkinson PET", "biological motion Parkinson *f*MRI", "biological motion Parkinson PET", "point light display Parkinson *f*MRI", "point light display Parkinson PET", "action observation Parkinson *f*MRI", "action observation Parkinson PET", "facial Parkinson *f*MRI" and "facial Parkinson PET". The preliminary pool of 870 retrieved studies, after duplicate removal, was evaluated based on title and abstract. The criteria for including studies in our *meta*-analysis were as follows: (Fig. 1):

1 Reports written in English.

2. Empirical studies using either functional magnetic resonance imaging (*f*MRI) or positron emission tomography (PET), excluding studies using other neuroimaging techniques (i.e., electroencephalography (EEG) and magnetoencephalography (MEG)) with different spatial and temporal resolution.

3. Studies based on whole-brain images and analyses, thus excluding reports of neuroanatomically more restricted analyses produced by the application of regions of interest (ROIs) or small volume correction (SVC) (Muller et al., 2018).

4. Studies on individuals diagnosed with PD, in which the presence and the severity of the impairment was assessed by means of the Unified Parkinson's Disease Rating Scale (UPDRS) (Goetz et al. 2007). We decided to include this selection criteria as a check for the clinical evaluation of PD, given that UPDRS is the most well-established scale for assessing disability and impairment of PD (Jankovic, 2008). Importantly, no studies were excluded for not fulfilling this criterion.

5. Studies reporting the results of within-group comparisons, between-group comparisons, or both. More specifically, we selected coordinates from: (i) within-group simple effects, or/and (ii) between-group comparisons (i.e., PD vs. HC). We included the within-group data into the analyses to get a better overview on whether a specific brain area was more strongly associated with one group than the other, while still showing activation in both groups, or else whether the same brain area was exclusively activated in just one group (e.g., Paulesu et al., 2014). By including coordinates from different types of contrasts (i.e., both between and within), we tried to maximize the number of included papers with a specific focus on social perception in each group.

6. Functional neuroimaging studies focused on social perception. More specifically, we ascertained to only include studies that reported statistical contrasts specifically targeting:

a) Human face and human action perception, involving the representation of other individuals. Therefore, we retained only tasks requiring participants to process stimuli eliciting a representation of others' actions and contrasting this with control conditions without human representation (Agosta et al., 2017), as well as tasks comparing the perception of faces versus non-meaningful mosaic-like colored patterns (Ramirez-Ruiz et al., 2008).

b) Direct comparisons between emotional stimuli and control stimuli (emotion > neutral in others; Heller et al., 2018). We included

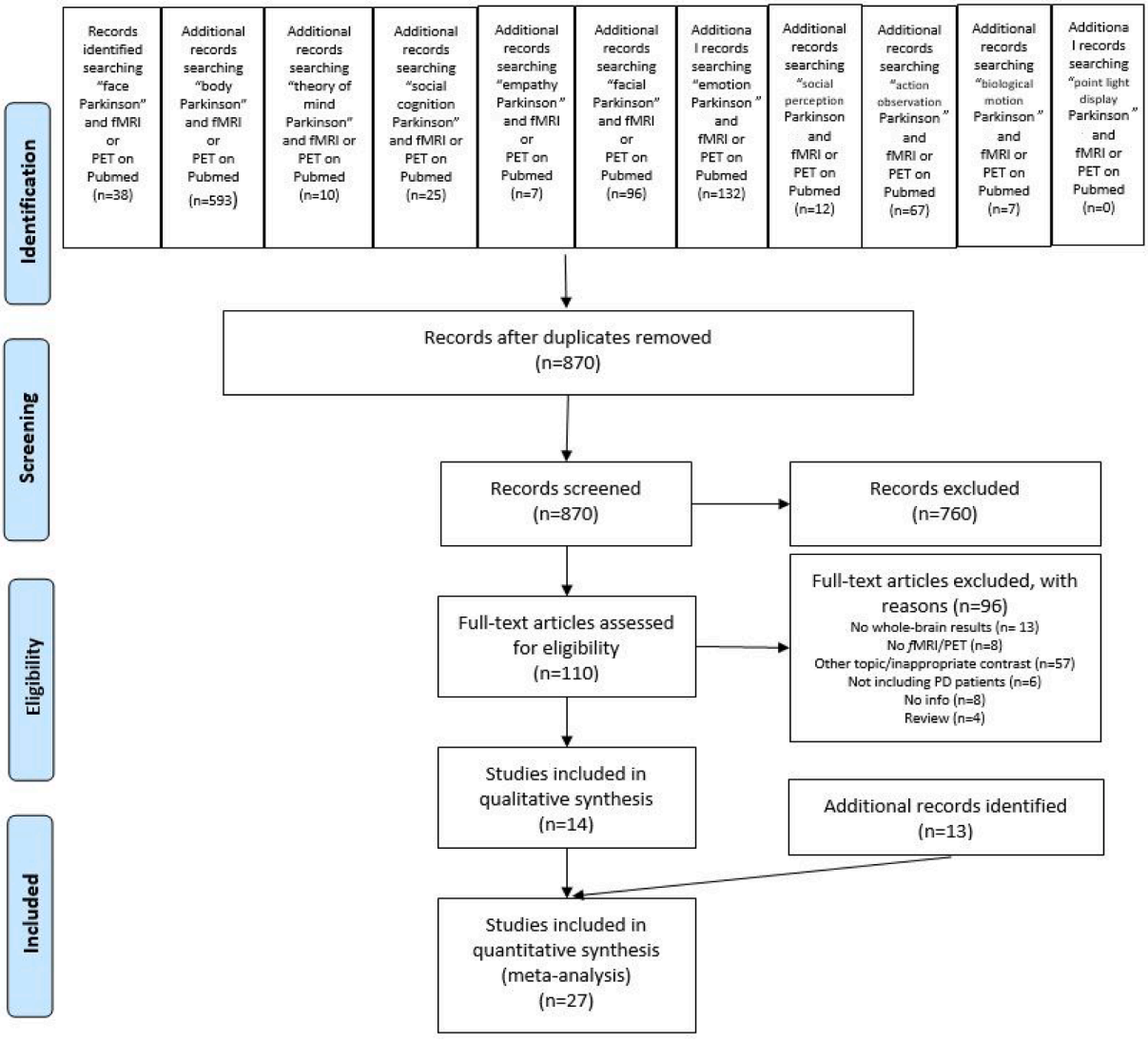

Fig. 1. PRISMA diagram depicting the selection process.

paradigms in which participants attended to emotional stimuli (e.g., faces expressing positive and/or negative emotions) aimed to elicit emotional processing (either explicit or implicit), and contrasting this kind of emotional representation with control conditions in which there was no emotional characterization (e.g., neutral faces; Wabnegger et al., 2015).

c) Positive correlations between brain activity and performance in social tasks (e.g., emotional facial recognition (EFR) task; Robert et al., 2014) or in neuropsychological tests assessing aspects related to social deficits (e.g., depression; Hu et al., 2015).

We excluded 760 irrelevant articles based on titles and abstracts. Closer full-text inspection of the remaining 110 articles according to the above selection criteria lead to the further exclusion of studies that did not employ *f*MRI or PET techniques (8 studies); review articles (4 studies); studies adopting either ROIs or SVC for statistical analyses (13 studies); studies not focusing on either PD patients (6 studies) or social perception (57 studies); studies not reporting essential information, such as x/y/z coordinates (8 studies). Fourteen studies in total fulfilled the above specified criteria.

We sought to increment the number of compatible studies by closely inspecting studies that did not enter our first-pass literature search but either quoted, or were quoted by, the 14 selected studies. We also closely inspected recent review articles and *meta*-analyses focused on cognitive processes in PD patients (Prenger et al., 2020; Solstrand Dahlberg et al., 2020). This second-pass search yielded 13 additional studies matching our inclusion criteria, thus increasing the total number of selected studies to 27 (Table 1). Of these 27 previously published studies, 25 studies reported activation foci for PD patients and could thus be included in the within-group ALE *meta*-analysis on PD patients (Table 1). These 25 studies provided 25 independent experiments (i.e. individual comparisons reported) with overall 455 PD subjects and 204 foci. In turn, 18 studies reported activation foci for healthy control individuals, and could enter the within-group ALE *meta*-analysis on healthy controls. These 18 studies provided 18 independent experiments, with overall 317 HC subjects and 196 foci (Table 1). The number of studies entering the two *meta*-analyses satisfied methodological recommendations on the ALE method (Eickhoff et al., 2016; Muller et al., 2018), particularly ensuring that results would not disproportionally represent just a few experiments (see also Zhang et al., 2019).

Another important methodological caveat is that the presence of more than one experiment including the same participants can undermine the validity of the *meta*-analytic results. To cope with this problem, we pooled the coordinates from all the relevant contrasts of a study as if they derived from just one experiment, thus effectively adjusting for within-group effects (Turkeltaub et al., 2002). This issue concerned 14 out of 27 studies.

Table 1
Overview of the 27 studies included in the *meta*-analysis on the neural bases of social perception in both patients with Parkinson disease (PD) and healthy control subjects (HC).

N	First author, year	Subjects	Mean age (years) and gender distribution of PD	Matching variables	Imaging technique	Stimuli	Task	Contrast	Foci PD	Foci HC	Group contrast
1	Agosta et al., 2017	25 PD; 19 HC	mean age: 66.5; 18 M and 7F	age and gender	*f*MRI	third-person videos	action observation task	action observation > baseline	2	10	PD vs. HC
2	Anders et al., 2012	8 PD; 8 HC	mean age: 58; 4 M and 4F	age and gender	*f*MRI	video clips	observation and imitation task	positive > neutral	5	5	PD; HC
3	Bell et al., 2019	13 PD; 12 HC	mean age: 66.31; 11 M and 2F	age and education	*f*MRI	emotional written words	affective go-NoGo task	emotion > control	–	1	HC > PD
4	Bommarito et al., 2020	33 PD; 22 HC	mean age: 70.33; no info on gender	age and education	*f*MRI	third-person videos	action observation task	action observation > baseline	22	26	HC; PD; HC > PD
5	Cardoso et al., 2010	16 PD; 18 HC	mean age: 62.5; 16 M	age	*f*MRI	face pictures	implicit emotional facial perception	face perception > control	1	–	PD > HC
6	Dan et al., 2019	25 PD; 32 HC	mean age: 64.7; 15 M and 10F	age, gender and education	*f*MRI	visual facial stimuli	emotional face matching task	negative emotion > control	2	–	PD > HC
7	Heller et al., 2018	25 PD; 31 HC	mean age: 62.4; 12 M and 13F	age	*f*MRI	videos	emotion recognition task	emotion > control	–	26	HC > PD
8	Hu et al., 2014	20 PD; 41 HC	mean age: 58.05; 9 M and 11F	age, gender and education	*f*MRI	verbal items	HDRS-17	association with depression	2	6	PD vs. HC
9	Knolle et al., 2020	23 PD; 17 HC	mean age: 63.1; 14 M and 9F	age, gender and education	*f*MRI	images	salience oddball task	emotion > neutral	4	4	PD vs. HC
10	Le Jeune et al., 2009	12 PD	mean age: 57.4; 8 M and 4F		PET	verbal items	AES	correlation with AES	5	–	PD
11	Lotze et al., 2009	9 PD; 10 HC	mean age: 65.7; 8 M and 1F	age	*f*MRI	videos of gestures	evaluation task	emotion > control	2	8	PD; HC; HC > PD
12	Moonen et al., 2017	19 PD; 19 HC	mean age: 60.2; 13 M and 6F	age, gender and education	*f*MRI	images from IAPS	evaluation task	emotion > control	26	23	PD; HC
13	Ory et al., 2017	16 PD; 16 HC	mean age: 56.2; 9 M and 7F	age, gender, handedness and education	PET	film excerpts	emotion elicitation task	correlation with decreased induction of disgust	12	–	PD
14	Peran et al., 2009	14 PD	mean age: 64.14; 8 M and 6F		*f*MRI	object drawings	generation of action-verbs	action > baseline	13	–	PD
15	Peran et al., 2013	10 PD	mean age: 60.3; no info on gender		*f*MRI	object drawings	generation of action-verbs	action > baseline	5	–	PD
16	Peron et al., 2010	13 PD; 13 HC	mean age: 53.3; 8 M and 5F	age, gender, handedness and education	PET	images	RMET	correlation with RMET performance	11	–	PD
17	Pohl et al., 2017	13 PD; 13 HC	mean age: 68; 8 M and 5F	age and education	*f*MRI	videos	emotion observation and execution tasks	emotion > baseline	7	21	PD; HC; HC > PD
18	Poisson et al., 2013	14 PD; 10 HC	mean age: 62; 9 M and 5F	age	*f*MRI	auditory and visual stimuli	action observation and execution	action > baseline	9	4	HC vs. PD
19	Politis et al., 2013	24 PD	mean age: 58.75; 21 M and 3F	age	*f*MRI	images	evaluation task	sexual > control	14	–	PD
20	Ramirez-Ruiz et al., 2008	20 PD; 10 HC	mean age: 72.75; 8 M and 12F	age, gender and education	*f*MRI	face pictures	detection task	face > control	5	4	PD; HC
21	Robert et al., 2014	36 PD	mean age: 58.6; no info on gender		PET	photographs	EFR task	correlation with EFR performance	6	–	PD
22	Rowe et al., 2002	12 PD; 12 HC	mean age: 62; 5 M and 7F	age	*f*MRI	auditory and visual stimuli	motor task	motor > rest	10	11	PD; HC; PD vs. HC
23					*f*MRI	videos			3	6	

(*continued on next page*)

Table 1 (*continued*)

N	First author, year	Subjects	Mean age (years) and gender distribution of PD	Matching variables	Imaging technique	Stimuli	Task	Contrast	Foci PD	Foci HC	Group contrast
	Sarasso et al., 2021	24 PD; 18 HC	mean age: 66.54; 17 M and 7F	age, gender and education			action observation task	action > baseline			PD vs. HC
24	Schienle et al., 2015	17 PD; 22 HC	mean age: 55.2; 9 M and 8F	age and education	*f*MRI	images	evaluation task	emotion > control	2	1	PD; HC
25	Snijders et al., 2011	10 PD; 21 HC	mean age: 60.2; 15 M and 9F	age and gender	*f*MRI	visual stimuli	imagery task	motor > baseline	9	20	PD; HC
26	Tessitore et al., 2002	10 PD; 10 HC	mean age: 59; 7 M and 3F	age, gender and education	*f*MRI	face pictures	emotion recognition task	emotion > control	20	18	PD; HC
27	Wabnegger et al., 2015	17 PD; 22 HC	mean age: 55.2; 9 M and 8F	age and education	*f*MRI	face pictures	evaluation task	emotion > control	7	2	PD vs. HC
									TOT FOCI: 204	**TOT FOCI: 196**	

Abbreviations: AES: Apathy Evaluation Scale; EFR: Emotional Facial Recognition; F: female; fMRI: functional magnetic resonance imaging; HDRS-17: Hamilton Depression Rating Scale; HC: healthy control; IAPS: International affective picture system; M: male; N, progressive study number; PD: Parkinson Disease; PET: Positron Emission Tomography; Sub, subjects; RMET: Reading The Mind In The Eye Task.

2.3. Activation likelihood estimation

We used the GingerALE software 3.0.2 (Eickhoff et al., 2009) to conduct a set of ALE analyses aiming at the identification of the brain areas associated with social perception in either PD patients, HC, or both groups. We followed the method described by Eickhoff et al. (2012), resulting in the same procedure reported in Arioli et al. (2021). In a first step, each of the activation coordinates derived from the selected studies, keeping separate those related to PD patients from the HC ones, was taken as the centre of a three-dimensional Gaussian probability distribution capturing the spatial uncertainty intrinsically associated with the coordinate data. All coordinates gathered from the selected studies that were not already in the MNI space were manually converted from the Tailairach to the MNI space by using the transformation tool supplied with GingerALE (Lancaster et al., 2007). The set of activation coordinates of each experiment was used to calculate probability distributions in the image space, which was then fitted in every voxel to yield a modeled activation (MA) map. The combination of the MA maps produced the ALE scores representing the convergence across experiments of activation in each brain voxel (Turkeltaub et al., 2002). In order to provide reliable statistical estimates (i.e. "true" convergence as opposed to random convergence), the ALE scores were contrasted against an empirically defined null distribution (Eickhoff et al., 2012). The null distribution is generated by random spatial association between experiments, with the distribution of foci within any given experiment maintained fixed. To this aim, a voxel was sampled at random from each MA map, and the union of the obtained values was calculated. This permutation was iterated 1,000 times and at each iteration the obtained ALE score was retained, yielding a densely sampled ALE null distribution. The comparison between the "true" and the null distribution effectively instantiates random-effects statistics, which represent the above-chance convergence across experiments, mitigating the possible preponderance of coordinate clustering in just one or in a small subset of experiments. To correct for multiple comparisons across voxels and protect against false positive errors, we adopted a $p < 0.05$ cluster-level threshold with family wise error type correction, with an uncorrected $p < 0.001$ cluster-forming threshold and 1,000 permutations (Eickhoff et al., 2012).

In a second analytical step, the significance maps that were separately obtained from, respectively, the PD and HC studies, were used to calculate direct comparisons between PD patients and HC, and the conjunction analyses across the two groups, to unveil, respectively, specific and common *meta*-analytic activation effects. This is accomplished by first generating a conjunction image, namely the voxel-wise minimum value across the ALE images for PD and HC, representing common brain activations in the two groups (Eickhoff et al., 2011). Subsequently, two ALE contrasts images were generated by directly subtracting one ALE image from the other. To correct for study size, GingerALE implements a random permutation of coordinates in two groups of the same size as the original datasets. A null distribution was generated by iterating a random permutation 1,000 times, each time subtracting the ALE images of the two simulated groups. The "true data" were then compared to the null distribution at every voxel. The ALE subtraction scores were converted to Z scores. For the between-group comparisons, given the unavailability of family wise error type corrected cluster-level inference in the GingerALE software (Hoffman and Morcom, 2018), we adopted a conventional uncorrected $p < 0.05$ threshold (as in previous publications, see for example, Alain et al., 2018; Gan et al., 2022; Huang et al., 2020; Papitto et al., 2020) and a minimum cluster volume size of 100 mm^3 with 1,000 permutations. For exploratory purposes, in order to also reveal possible increased or decreased *meta*-analytic activation effects showing a trend towards statistical significance, we also run the within-group analyses adopting a slightly less conservative statistical threshold of < 0.1 cluster-level threshold with family wise error type correction, with an uncorrected $p < 0.001$ cluster-forming threshold and 1,000 permutations. This less conservative threshold then also constituted the input for the between-group comparisons for which, as previously noted, family wise error type correction is unavailable in GingerALE, and where we therefore again used a conventional uncorrected $p < 0.05$ threshold and a minimum cluster volume size of 100 mm^3 with 1,000 permutations.

3. Results

3.1. Social perception in patients with Parkinson disease

Social perception processes in PD patients recruited consistent activation in the right middle temporal gyrus and in the fusiform gyrus bilaterally, alongside the right posterior cerebellum (lobule VI) (Fig. 2**a;** Table 2). Further *meta*-analytic activations were found in the left inferior and middle occipital cortex.

3.2. Social perception in healthy control individuals

Activation associated with social perception in HC were subcortical and involved the putament and pallidus in the left hemipshere (Fig. 2**b;**

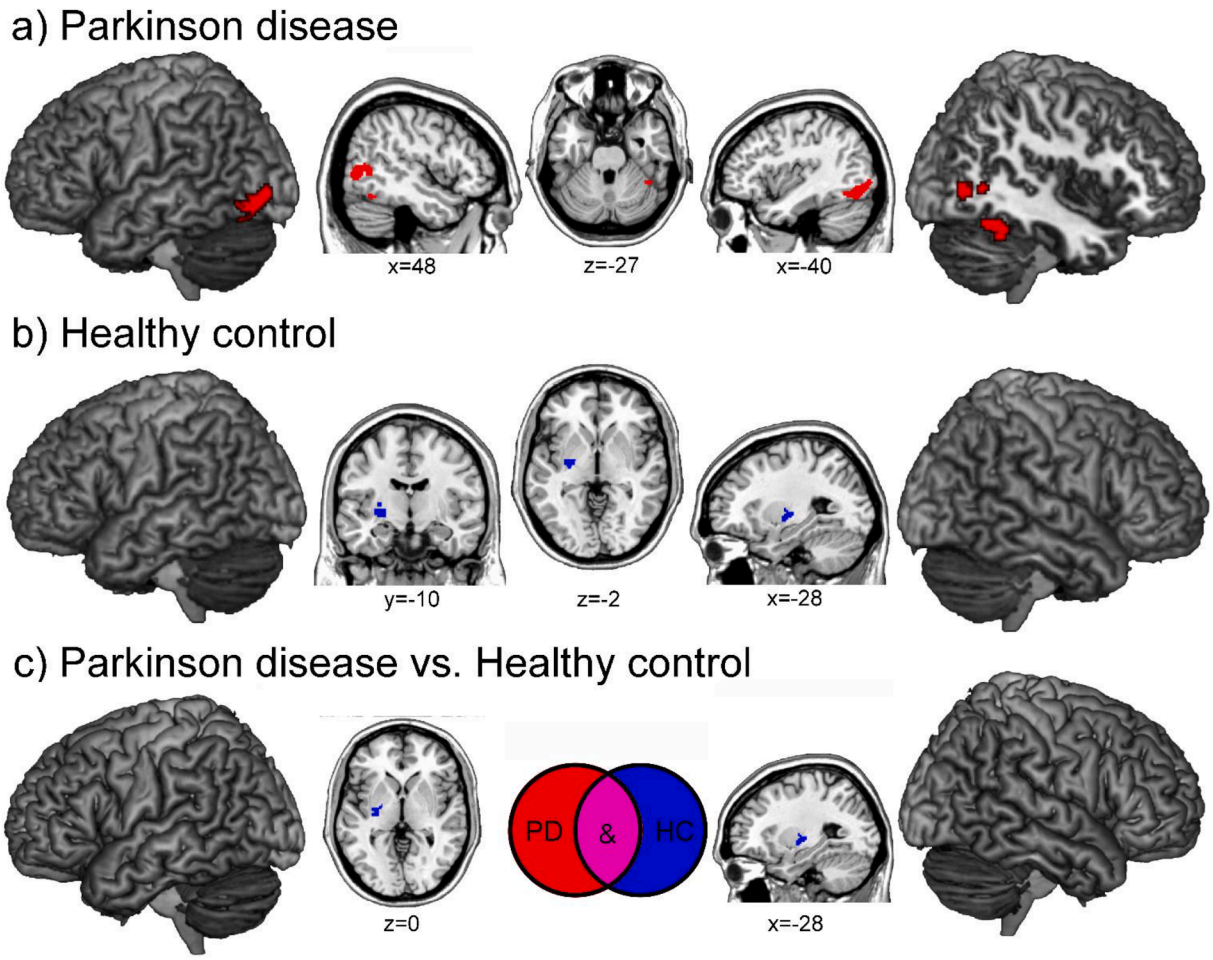

Fig. 2. The neural bases of social perception processes in patients with Parkinson disease (PD), healthy control (HC) individuals, and the brain differences between the two groups. The figure displays the areas consistently active during social perception tasks in PD (a), HC subjects (b), and specific brain responses in the two groups (c).

Table 2
Brain areas consistently active during social perception processes in individuals with Parkinson disease (PD). From left to right, the table reports the cluster number, the cluster volume size (in mm^3), the stereotaxic Montreal Neurological Institute (MNI) coordinates of local maxima (in mm) and anatomical labeling of the significant clusters. Anatomical labeling of clusters was derived from GingerALE (Eickhoff et al., 2012) and were checked using the SPM Anatomy Toolbox (v.2.2c; Eickhoff et al., 2005). We adopted a cluster-level $p < 0.05$ threshold, corrected for family wise error (FWE).

Cluster #	Volume (mm^3)	x	y	z	Brain region
1	2088	−44	−74	−8	Left inferior occipital gyrus
		−42	−86	−2	Left middle occipital gyrus
		−40	−64	−14	Left fusiform gyrus
2	1608	48	−72	0	Right inferior occipital gyrus
		52	−62	8	Right middle temporal gyrus
3	776	44	−50	−22	Right fusiform gyrus/Right cerebellum lobule VI

Table 3).

3.3. Social perception in Parkinson disease patients versus healthy controls

We found no significant overlapping activation for social processing in PD patients and HC individuals (Fig. 2**c;** Table 4). Also, the direct comparison analysis highlighted no significant stronger activation during social perception tasks in PD patients compared with HC subjects (Fig. 2**c;** Table 4). In turn, the reverse comparison revealed significant effects for HC subjects compared to PD patients in left putamen and left pallidus (Fig. 2**c;** Table 4).

Table 3
Brain areas consistently active during social perception processes in the healthy control (HC) group. From left to right, the table reports the cluster number, the cluster volume size (in mm^3), the stereotaxic MNI coordinates of local maxima (in mm) and anatomical labeling of the significant clusters. Anatomical labeling of clusters was derived from GingerALE (Eickhoff et al., 2012) and were checked using the SPM Anatomy Toolbox (v.2.2c; Eickhoff et al., 2005). We adopted a cluster-level $p < 0.05$ threshold, corrected for family wise error (FWE).

Cluster #	Volume (mm^3)	x	y	z	Brain region
1	720	−30	−10	−2	Left putamen/Left pallidum

3.4. Exploratory analyses

Whereas for patients with PD we did not find any additional within-group clusters of activation even in the analysis using a less conservative $p < 0.1$ family wise error corrected threshold (Fig. 3**a,** Table 5), for healthy control individuals we found a trend toward consistent within-group brain activity in the left IPL, extending into the intraparietal sulcus (IPS) and into the left postcentral gyrus (Fig. 3**b;** Table 5). In agreement with these within-group findings, also in the between-group contrast analysis, the left inferior parietal cortex appeared to be more

Table 4
Brain areas displaying common and different activation in the Parkinson disease (PD) and healthy control (HC) groups during social perception processes. From left to right, the table reports the cluster number, the cluster volume size (in mm^3), the stereotaxic MNI coordinates of local maxima (in mm) and anatomical labeling of the clusters for the conjunction analysis (top), for the specific effects in PD compared to HC (middle), and for the specific effects in HC compared to PD (bottom). Anatomical labeling of clusters was derived from GingerALE (Eickhoff et al., 2012) and were checked using the SPM Anatomy Toolbox (v.2.2c; Eickhoff et al., 2005). We adopted a cluster level $p < 0.05$ threshold and a minimum cluster volume size of 100 mm^3.

Patients with Parkinson disease & Healthy control individuals					
N.A.					
Patients with Parkinson disease > Healthy control individuals					
N.A.					
Healthy control individuals > Patients with Parkinson disease					
Cluster #	Volume (mm^3)	x	y	z	Brain region
1	720	−28	−13	0	Left putamen/Left pallidum

strongly active in HC than in patients with PD (Fig. 3**c;** Table 5). No other additional results were found in the exploratory analyses.

4. Discussion

Several behavioral studies have investigated social processes in PD patients (Bek et al., 2021; Prenger et al., 2020). In turn, only a few studies have focused on the neural correlates of social perception deficits in PD patients, with rather inconsistent results. Here, we used a coordinate-based neuroimaging *meta*-analysis procedure to highlight the consistency in the available findings. This is the first neuroimaging *meta*-analysis that aimed to clarify the neural bases of social perception impairments in PD patients. We expected to find a decreased activation in the frontal cortex and in the basal ganglia and possibly an increased activity in the cerebellum in PD patients, compared to HC participants.

4.1. Social perception in PD patients

Our results show that during social perception tasks PD patients reveal consistent activations in a bilateral network involving the middle and inferior occipital gyri and the fusiform gyrus, as well as the right middle temporal gyrus and the right posterior cerebellum (lobule VI).

Brain responses elicited by social perception tasks have been previously found in the temporal and fusiform cortex of PD patients (e.g., Pohl et al., 2017; Schienle et al., 2015), in agreement with our results. It is well known that the fusiform gyrus plays a fundamental role in face processing (McGugin et al., 2020; Papagno et al., 2021; Kanwisher and Yovel, 2006). Other regions in the middle and superior temporal sulcus are crucially involved in social perception, and particularly in the perception of biological motion involving body parts such as faces, hands, and postures of conspecifics (Papeo et al., 2019; Reader and Holmes, 2019; Tsantani et al., 2019).

Our data are also consistent with increasing evidence showing the involvement of the posterior (lateral) cerebellum in social perception tasks (Cattaneo et al., 2021; Clausi et al., 2021; Leggio & Olivito, 2018; Van Overwalle et al., 2019a; 2020), as suggested also by connectivity

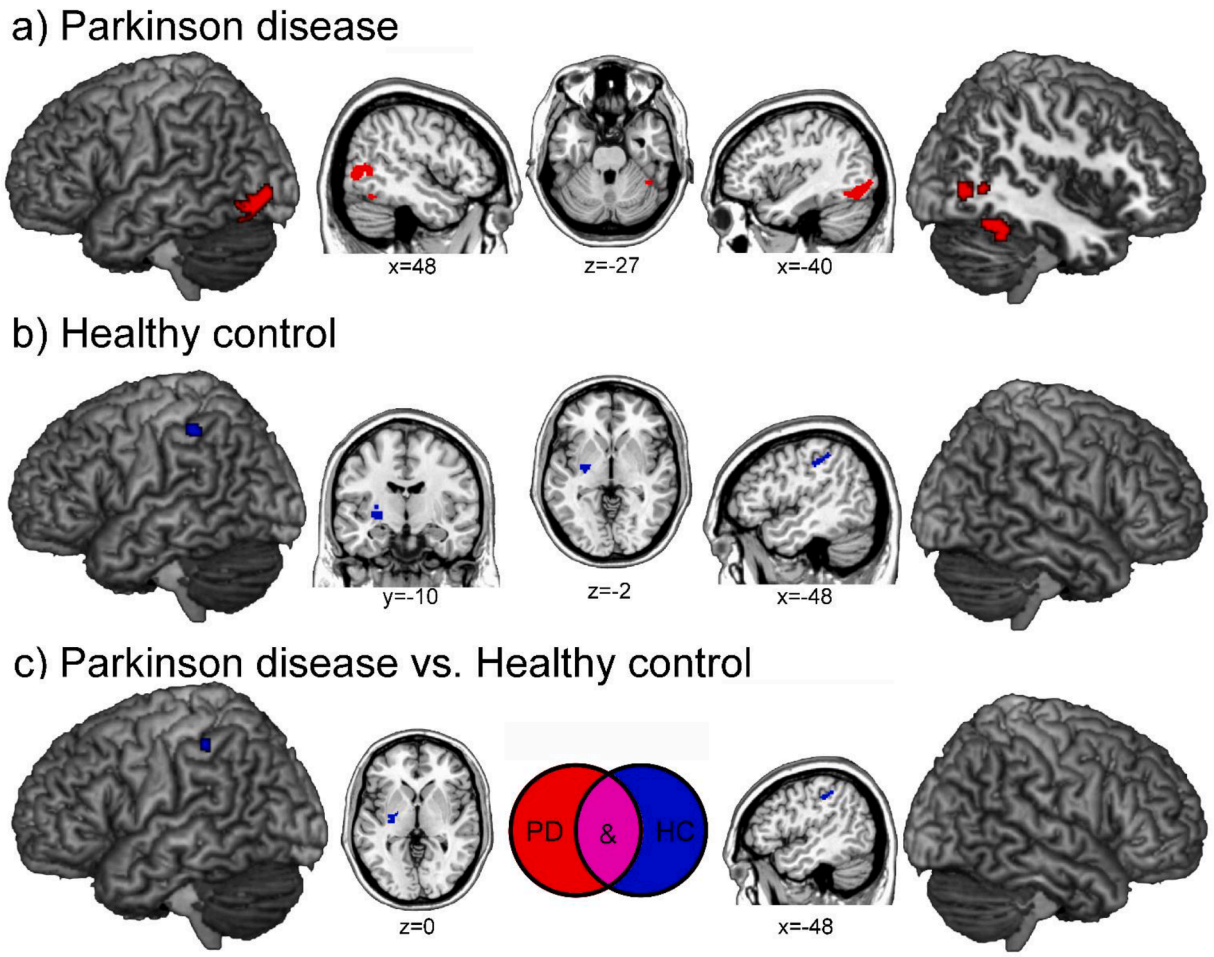

Fig. 3. Exploratory analysis on the neural bases of social perception processes in patients with Parkinson disease (PD), healthy control (HC) individuals, and the brain differences between the two groups. The figure displays the areas consistently active during social perception tasks in PD (a), HC subjects (b), and specific brain responses in the two groups (c).

Table 5
Exploratory analysis to investigate statistical trends with a less conservative threshold. From left to right, the table reports the cluster number, the cluster volume size (in mm^3), the stereotaxic MNI coordinates of local maxima (in mm) and anatomical labeling of the clusters for the individual *meta*-analysis on PD (top), HC (middle) and for the contrast analysis comparing HC and PD (bottom). Anatomical labeling of clusters was derived from GingerALE (Eickhoff et al., 2012) and was checked using the SPM Anatomy Toolbox (v.2.2c; Eickhoff et al., 2005). For the single database *meta*-analyses, we adopted a cluster-level $p < 0.1$ threshold, corrected for family wise error (FWE). For the contrast analysis, we adopted a cluster level $p < 0.05$ threshold and a minimum cluster volume size of 100 mm^3.

Patients with PD

Cluster #	Volume (mm^3)	x	y	z	Brain region
1	2088	−44	−74	−8	Left inferior occipital gyrus
		−42	−86	−2	Left middle occipital gyrus
		−40	−64	−14	Left fusiform gyrus
2	1608	48	−72	0	Right inferior occipital gyrus
		52	−62	8	Right middle temporal gyrus
3	776	44	−50	−22	Right fusiform gyrus/Right cerebellum lobule VI

Healthy control individuals

Cluster #	Volume (mm^3)	x	y	z	Brain region
1	720	−30	−10	−2	Left putamen/Left pallidum
2	584	−50	−38	48	Left inferior parietal lobule/ Left intraparietal sulcus
		−46	−26	40	Left postcentral gyrus

Patients with Parkinson disease & Healthy control individuals
N.A.

Patients with Parkinson disease > Healthy control individuals
N.A.

Healthy control individuals > Patients with Parkinson disease

Cluster #	Volume (mm^3)	x	y	z	Brain region
1	720	−28	−13	0	Left putamen/Left pallidum
2	280	−48	−34	44	Left inferior parietal lobule/ Left intraparietal sulcus

studies showing bidirectional closed loops between the posterior cerebellar lobe and the mentalizing network (van Overwalle et al., 2019b). In particular, we found a specific activation in the lobule VI. Lobule VI to Lobule IX represent the posterior cerebellar lobe, which is separated by the primary fissure from the anterior lobe (lobules I-V) and by the posterolateral fissure from the flocculonodular lobe (lobule X). The posterior lobe (particularly lobules VI and VII) has been associated with language, spatial, executive, working memory, and social-affective tasks (Stoodley and Schmahmann, 2010), rather than motor tasks (Stoodley et al., 2012). The role of the cerebellum in social prediction and social perception in healthy participants has been recently supported by noninvasive brain stimulation (e.g., Ferrari et al., 2019a, 2019b, 2021; Heleven et al., 2021; Oldrati et al., 2021) and neuroimaging data (e.g., Heleven et al., 2019; Schraa-Tam et al., 2012; Van Overwalle et al., 2019a; b; c; 2020).

A general role of the posterior cerebellum in social cognition has been assumed in relation to supporting optimal predictions about social interactions (van Overwalle et al., 2020). In the motor domain, motor sequence predictions are created by the cerebellum and are then compared with feedback signals from external inputs. In this way, online adjusting of motor action execution becomes possible (Ito, 2008). It is nowadays acknowledged that the cerebellum constructs internal models also for purely mental states, without movements or somatosensory feedback (Leggio & Molinari, 2015; Van Overwalle et al., 2019a; 2020). In this view, the posterior cerebellum may be involved in the processing of social stimuli by providing internal models of social interactions, thus allowing predicting/anticipating others' behaviors in the social environment (Van Overwalle et al., 2019a; b; Oldrati et al., 2021). Recently, also data from neuropsychological studies in children with congenital (Urgesi et al., 2021) and acquired (Butti et al., 2020) cerebellar damage supported the role of the cerebellum in social prediction. Nevertheless, as discussed in the Introduction, the exact nature of increased cerebellar activation in PD remains elusive, with contrasting interpretations favoring either beneficial compensatory mechanisms (Wu and Hallett, 2013) or motor dysfunction (Martinu and Monchi, 2013).

4.2. Social perception in healthy controls

During social perception tasks, HC subjects displayed consistent activation in left basal ganglia.

In addition to their motor function, the basal ganglia also subserve cognitive functions (Afifi, 2003; Simonyan, 2019; Tettamanti et al., 2005). Previous studies have pointed to a critical role of basal ganglia in social cognition processes such as emotion regulation and recognition as well as reward processing (Buot et al., 2013; Ceravolo et al., 2021; for review see Eisinger et al., 2018; Pierce and Peron, 2020). The basal ganglia, through the selection of relevant and the filtering of irrelevant emotional stimuli (Florio et al., 2018), promote quick and appropriate behavioral responses (Pierce and Peron, 2020). The continuous repetition of these selection process (relevant vs. irrelevant stimuli) leads to a reinforcement of neural emotional responses, which may become largely automatic (Pierce and Peron, 2020).

4.3. Commonalities and differences between PD patients and HC during social perception tasks

We found greater activation in healthy subjects compared to PD patients in the left basal ganglia. In turn, patients with PD had no greater activation than controls. Also, we did not find any common significant activation between patients with PD and healthy control individuals during social processing in brain areas related to recognition of social signals. However, this latter finding likely depends on the limited number of available studies reducing statistical power (for similar results, see Vucurovic et al., 2020; Zhang et al., 2019).

Social impairments are frequent in several basal ganglia disorders (e.g. in Huntington's disease, Parkinson's disease, and Tourette's syndrome) and have been associated with fronto-striatal dysfunctions (Bodden et al., 2010; Roca et al., 2010). Different studies showed that the beta rhythms in basal ganglia during action perception are partially overlapping with the changes reported during action execution (Alegre et al., 2010; Foffani et al., 2005; Marceglia et al., 2009), supporting the idea that basal ganglia may support mirror network patterns of activation (Alegre et al., 2011; Errante & Fogassi, 2020). Both neuroimaging findings (Anders et al., 2012; Pohl et al., 2017) and neuropsychological studies (Nobis et al., 2017) support the idea that socio-emotional symptoms in PD are explained by a mirror network alteration, involving also the basal ganglia (Farina et al., 2020).

There is converging evidence that the posterior cerebellum may provide compensatory support to the dysfunctional basal ganglia in PD patients (Lewis et al., 2013; Mirdamadi, 2016; Solstrand Dahlberg et al., 2020; Wu and Hallett, 2013; Yu et al., 2007). Accordingly to our result, several studies included in our *meta*-analysis showed posterior cerebellum activations in PD patients (e.g., Agosta et al., 2017; Ory et al., 2017; Poisson et al., 2013). Although the direct comparison targeting stronger *meta*-analytic activations in PD than in HC did not yield any significant effects in the posterior cerebellum (possibly due to the limited sample size, see Rotge et al., 2010; Shao et al., 2015; Wei et al., 2016), at a qualitative level, we found an activation of the right posterior cerebellum when PD patients were analyzed alone, whereas no comparable activation was found in HC subjects. Based on these qualitative differences alone, and due to the lack of a significant *meta*-analytic effect

in the direct comparison, a strong claim for compensatory cerebellar activation in PD patients is not supported. Further evidence in larger study and *meta*-analytic samples is required to better elucidate this issue.

4.4. Exploratory analyses

Using a less conservative threshold, we found that, during social tasks, healthy control subjects displayed a trend towards significant activation in the left IPL, alongside the left IPS and the left postcentral gyrus. A trend towards a statistically significant activation increase for HC compared to patients with PD in the left IPL and IPS also emerged in the between-group analysis.

Previous neuroimaging experiments suggested that the parietal cortex is involved in the processing of social and emotional information in HC (Marrazzo et al., 2021). A causal role for the parietal cortex in social perception was also supported by the results of a *meta*-analysis on brain lesion studies (Urgesi et al., 2014).

It has been shown that visual processing of facial emotional expressions leads to activations in the IPL (Kitada et al., 2010; Sarkheil et al., 2013). The IPS seems to support the adaptive online control of actions (Dafotakis et al., 2008; Medina et al., 2020) and is involved in action goal coding (Gardner et al., 2015). Both action perception and action execution are represented in the IPS (Bruni et al., 2018). Moreover, the IPS is also involved in face processing (Zhen et al., 2013) and emotion differentiation (Camacho et al., 2019). All these socio-emotional processes are supported by the basic mirror neuron mechanisms, which allow to respond to social stimuli of conspecifics with an internal brain representation of their movements and actions (Rizzolatti and Rozzi, 2018).

Our results, although only trendwise, thus confirm the hypothesis of an impairment of the mirror neuron resonance system in patients with PD. Lesions of IPL/IPS extending to the somatosensory areas and supramarginal gyrus can lead to social perception deficits (Medina et al., 2020). Furthermore, decreased activation and connectivity patterns between the IPL, primary motor cortex, and supplementary motor area (SMA) in patients with PD were shown during both resting state conditions (Luo et al., 2015) and motor tasks (Wu and Hallett, 2005), probably reflecting an impairment in the neural systems supporting motor preparation and initiation (Tessitore et al., 2014). The posterior part of the superior temporal sulcus (pSTS) represents the visual input of the human mirror neuron system, from pSTS the information is forwarded to the parietal cortex (Gardner et al., 2015). Finally, information is forwarded to the inferior frontal gyrus and the ventral premotor cortex, where action goals are coded (Iacoboni and Dapretto, 2006). Thus, deactivation of mirror neuron areas in the parietal cortex may be one reason for a deficit in the neural mechanism for social resonance, and may consequently be a putative basis for impaired social perception in PD (Pohl et al., 2017; see also Ricciardi et al., 2017). However, considering that our results only represent a statistical trend, more solid evidence is required to support this interpretation.

4.5. Possible confounding variables

Considering variability of both clinical conditions and clinical treatment (e.g., levodopa equivalent daily dose) between different patients with PD, it would be important to consider these aspects when investigating the neural outcomes of PD. Particularly, the type of dopaminergic treatment, the use of deep brain stimulation, and a predominant left side motor symptom onset seem to have a noticeable effect on social processing in PD (e.g., Coundouris et al., 2019). Unfortunately, considering the low number of studies focused on social perception on PD, we were not able to contrast studies with different medication conditions, nor to select only studies using a specific medication condition. Moreover, even within an individual study there can be heterogeneity in the medication status of PD patients (e.g., Bell et al., 2019). Most of the studies included in our *meta*-analysis did not report the side of motor symptom onset, nor information regarding treatment with deep brain stimulation. This is probably why also in other *meta*-analyses on PD these aspects were not considered (e.g., Solstrand Dahlberg et al., 2020). The lack of control for these clinical variables, however, represents a limitation of our results. For clarity, we provide a table in the Supplementary Materials with information pertaining to these clinical aspects for each study (**Table S1**).

4.6. Conclusion and future directions

In conclusion, our results suggest that social perception deficits in PD patients involve the left basal ganglia, and we also found a trend toward a decreased activity in the mirror system areas. An important question for future research regards the putative compensatory role of the posterior cerebellum in PD.

At a practical level, our results can guide the design and the implementation of neuro-psychological training programs for PD patients, supporting the crosstalk between basic scientists and clinical researchers (Blandini, 2013). Action observation training (AOT) in PD patients enhanced the execution of spontaneous movements (Castiello et al., 2009; Pelosin et al., 2013), and observing and performing a target movement simultaneously aids patient performance (Tremblay et al., 2008). This could happen since these trainings lead to a stronger activation of the brain network that subtends motor control (Caligiore et al., 2017), which is minimally damaged in the first stages of PD (e.g., Poliakoff, 2013). This stronger activation may cause a brain system reinforcement, compensating the alterations in motor execution areas. Based on our results, it might be useful to add social stimuli to this training (e.g., images or video clips depicting emotional faces, interacting people, social gestures), promoting the observation and imitation of social behavior, so that PD patients could counteract the deterioration of simulation systems underlying social perception. Critically, the effects of this type of social training may be further enhanced by combining the behavioral approach with posterior cerebellar non-invasive stimulation to boost the compensatory effect of cerebellum activity (e.g., Manto et al., 2021; Cattaneo et al., 2021; see also Chen and Chen, 2019 for a review on the possible benefit in using non-invasive brain stimulation in PD).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2022.103031.

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