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Functional alterations in resting-state networks for Theory of Mind in Parkinson's disease

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Abstract

In Parkinson's disease (PD), impairment of Theory of Mind (ToM) has recently attracted an increasing number of neuroscientific investigations. If and how functional connectivity of the ToM network is altered in PD is still an open question. First, we explored whether ToM network connectivity shows potential PD-specific functional alterations when compared to healthy controls (HC). Second, we tested the role of the duration of PD in the evolution of functional alterations in the ToM network. Between-group connectivity alterations were computed adopting resting-state functional magnetic resonance imaging (rs-fMRI) data of four groups: PD patients with short disease duration (*PD-1*, $n = 72$); PD patients with long disease duration (*PD-2*, $n = 22$); healthy controls for PD-1 (*HC-1*, $n = 69$); healthy controls for PD-2 (*HC-2*, $n = 22$). We explored connectivity differences in the ToM network within and between its three subnetworks: Affective, Cognitive and Core. PD-1 presented a global pattern of decreased functional connectivity within the ToM network, compared to HC-1. The alterations mainly involved the Cognitive and Affective ToM subnetworks and their reciprocal connections. PD-2—those with longer disease duration—showed an increased connectivity spanning the entire ToM network, albeit less consistently in the Core ToM network, compared to both the PD-1 and the HC-2 groups. Functional connectivity within the ToM network is altered in PD. The alterations follow a graded pattern, with decreased connectivity at short disease duration, which broadens to a generalized increase

Abbreviations: ADNI, Alzheimer's Disease Neuroimaging Initiative; Amyg, amygdala; aToM, Affective Theory of Mind; CoreToM, Core Theory of Mind; cToM, Cognitive Theory of Mind; dACC, dorsal anterior cingulate cortex; dATL, dorsal anterior temporal lobe; dlPFC, dorsolateral prefrontal cortex; dMPFC, dorsomedial prefrontal cortex; HC, healthy controls; ILFC, infero-lateral frontal cortex; IPL, inferior parietal lobule; MoCA, Montreal Cognitive Assessment; OFC, orbitofrontal cortex; PD, Parkinson's disease; PD-1, Parkinson's disease patients with short disease duration; PD-2, Parkinson's disease patients with long disease duration; PPMI, Parkinson's Progression Markers Initiative; Prec, precuneus; rs-fMRI, resting-state functional magnetic resonance; STS, superior temporal sulcus; ToM, Theory of Mind; TPJ, temporo-parietal junction; vACC, ventral anterior cingulate cortex; vATL, ventral anterior temporal lobe; vMPFC, ventromedial prefrontal cortex.

with longer disease duration. The alterations involve both the Cognitive and Affective subnetworks of ToM.

KEYWORDS
functional connectivity, Parkinson's disease, resting state, Theory of Mind

1 | INTRODUCTION

Parkinson's disease (PD) (Bellucci et al., 2016) is a neurodegenerative disorder primarily associated with motor-symptom manifestations, such as tremors, rigidity, bradykinesia and gait difficulties. However, the entire neurological condition is more complex, extending to non-motor symptoms, psychiatric and psychological manifestations, as well as cognitive dysfunctions (Jankovic, 2008; Obeso et al., 2017; Papagno & Trojano, 2018; Trojano & Papagno, 2018). The full spectrum of cognitive profiles has been described in these patients, ranging from subjective cognitive decline to mild cognitive impairment (MCI) or dementia (Aarsland et al., 2001; Papagno & Trojano, 2018; Perez et al., 2012; Petersen et al., 2014). The cognitive domains typically affected in PD by cognitive impairments (CI) are executive-attentional functions, visuo-spatial abilities and long-term memory, as well as language (Barone et al., 2011; Kehagia et al., 2010; Martinez-Horta & Kulisevsky, 2019; Muslimović et al., 2005) and social cognition (Bora et al., 2015).

Social cognition ranges from low-level perceptual processes of self-other discrimination (e.g. perception of social cues conveyed by sensory-related stimuli) to higher-order processes involving the representation and attribution of mental and emotional states to self and others. These latter functions are commonly referred to as Theory of Mind (ToM). Compelling evidence suggests that ToM is not a unitary phenomenon, but rather comprises dissociable, albeit interacting, features. Indeed, we can distinguish a cognitive (i.e. represent and attribute beliefs, thoughts, intentions and desires) from an affective (i.e. represent and attribute emotions) ToM, partially dissociable at both the behavioral and neural levels (Campanella et al., 2022; Corradi-Dell'Acqua et al., 2020; Kalbe et al., 2010; Rossetto et al., 2018; Shamay-Tsoory et al., 2005; Simone G. Shamay-Tsoory & Aharon-Peretz, 2007).

Behavioral evidence of ToM impairment in PD has been frequently reported (Trompeta et al., 2021), but if and how the cognitive and affective ToM might be specifically affected, both at behavioural and neural levels, is still the subject of controversy. Crucially, recent partially conflicting findings suggest either an early deterioration of cognitive ToM alone or a general decline of both affective and cognitive ToM beginning with the early stages of the disease (Bodden, Dodel, & Kalbe, 2010; Bodden, Mollenhauer, et al., 2010; Bora et al., 2015; Christidi et al., 2018; Coundouris et al., 2020; Narme et al., 2013; Santangelo et al., 2012).

At this point, after several decades since the origin of the term ToM (Premack & Woodruff, 1978), a distributed neural network underlying these skills has been identified. The Abu-Akel and Shamay-Tsoory (2011) neuroanatomical model of ToM includes specific cognitive and affective subnetworks. According to this model, the *affective ToM* (aTOM) subnetwork involves the amygdala (Amyg), the ventral striatum (nucleus accumbens), the ventral anterior cingulate cortex (vACC), the orbitofrontal cortex (OFC), the ventral anterior temporal lobe (vATL), the ventromedial prefrontal cortex (vMPFC) and the infero-lateral frontal cortex (ilFC). Conversely, the *cognitive ToM* (cTOM) subnetwork comprises the dorsal striatum (caudate and pallidum), the dorsal ATL (dATL), the dorsal ACC (dACC), the dorsomedial PFC (dMPFC) and the dorsolateral PFC (dlPFC). Moreover, a set of regions—*the Core ToM* (coreToM) subnetwork—appears to support both affective and cognitive circuits. This Core ToM system serves as an initial gateway to assessing agency in ToM and comprises the temporo-parietal junction (TPJ), the superior temporal sulcus (STS) and the precuneus (Prec).

The progressive dopamine depletion in PD, involving not only the basal ganglia networking but also the fronto-parietal and limbic circuits (Obeso et al., 2008), influences key regions of the ToM network. While it has been hypothesized that the dopaminergic alteration in PD might be linked to ToM-related impairment (Shamay-Tsoory et al., 2005; Yoshimura et al., 2005), to date, only a handful of neuroimaging studies have investigated how the anatomical and functional correlates of ToM in PD (Trompeta et al., 2021) might be modified by the disease.

Cognitive ToM deficits have been linked to grey-matter volume decrease of the precentral and post-central gyri, the middle-frontal and inferior-frontal gyri and the anterior cingulate gyrus (Díez-Cirarda et al., 2015), as well as to decreased white-matter volume of the superior frontal fasciculus and white-matter volume adjacent to the frontal lobe, which indicate altered fronto-parietal

anatomical connectivity (Díez-Cirarda et al., 2015). Conversely, no clear evidence is available of volume decreases in the aToM subnetwork (Nigro et al., 2016).

Overall, it is likely that the anatomical modifications in PD of the brain circuitry mediating ToM abilities might also lead to an alteration of functional connectivity level, as measured with resting-state connectivity (rs-fMRI). Yet, a description of the rs-fMRI connectivity of the ToM network in PD has not been reported.

The present study aims to describe the rs-fMRI connectivity of ToM network in PD. First, we explore whether the Affective, Cognitive and Core ToM subnetworks show potential PD-specific functional alterations when compared with healthy controls (HC), including a large sample of PD patients (PD-1 group) from the Parkinson's Progression Marker Initiative (PPMI) (Marek et al., 2011). Second, we test the role of disease duration in the manifestation of functional alterations in ToM subnetworks by considering a second subpopulation of PD (PD-2 group) with longer disease duration.

2 | METHODS

2.1 | Participants

We considered four experimental groups, comprising subjects for which both a T1 anatomical image and rs-fMRI data were available. MRI scanning parameters for each dataset are described in Supporting Information considered the following datasets:

1. PD patients with short disease duration (*PD-1*, $n = 72$);
2. PD patients with long disease duration (*PD-2*, $n = 22$);
3. Healthy control group for PD-1 (*HC-1*, $n = 69$);
4. Healthy control group for PD-2 (*HC-2*, $n = 22$).

Table 1 summarizes the demographic information and clinical features of the different experimental groups. Data for PD-1 was extracted from the Parkinson's Progression Markers Initiative (Marek et al., 2011) (PPMI) (freely available online at www.ppmi-info.org/study-design). Data of the PPMI project have been collected at research centres around the world (in the United States, Europe and Australia) using a standardized protocol. Data from the PPMI dataset were extracted between 6 June and 19 July 2022 in accordance with the PPMI's Data Use Agreement. Inclusion criteria were (1) age 50–80 years old; (2) diagnosis of Parkinson's (PD code in the dataset); and (3) availability of structural MRI and rs-fMRI.

For the second aim of the current study (i.e. to test the role of disease duration in the manifestation of functional alterations in the ToM networks), we included a second dataset (PD-2), comprising PD patients with longer disease duration, recruited in our centre (the Interdepartmental Center for Mind/Brain Sciences, CIMeC, University of Trento) in which rsfMRI was carried out in a closed-eye condition. All participants had normal or corrected-to-normal vision and read and signed an informed consent to participate in the study. The study was assessed and validated by the university Ethics Committee.

TABLE 1 Demographics and clinical characteristics of the experimental groups. Values represent mean, with standard deviation in brackets. PD patients were assessed in medication-ON condition. We found data for the Montreal Cognitive Assessment (MoCA) for 54 patients in PD-1 and 21 patients in PD-2 (noted by asterisks).

	PD-1 ($n = 72$)	HC-1 ($n = 69$)	PD-2 ($n = 22$)	HC-2 ($n = 22$)	Statistics	Post hoc
Sex	20 F, 52 M	51 F, 18 M	10 F, 12 M	15 F, 7 M	$X_3 = 32.88$, $p < 0.0001$	PD1 vs. HC1 ($Z = 5.4$, $p < 0.001$) PD1 vs. HC2 ($Z = 3.4$, $p < 0.001$) PD2 vs. HC1 ($Z = 2.4$, $p = 0.01$)
Age	67.10 [5.71]	67.72 [2.58]	66.32 [7.01]	70.72 [8.59]	$F_3 = 3.001$, $p = 0.03$	HC2 > HC1 ($t_{89} = 2.6$, $p = 0.01$) HC2 > PD1 ($t_{92} = 2.3$, $p = 0.02$)
Disease duration in years	2.11 [1.46]	—	7.43 [5.01]	—	$t_{92} = 7.74$, $p < 0.0001$ *PD2 > PD1*	—
Hoehn and Yahr stage	1.64 [0.54]	—	1.7 [0.56]	—	$t_{92} = 0.99$, $p = 0.32$	—
MoCA	25.44 [3.45] *54 PD	—	22.86 [4.26] *21 PD	—	$t_{73} = 2.84$ $p = 0.005$ *PD-1 > PD-2*	—

Abbreviations: HC-1, healthy control, large group; HC-2, healthy controls, small group; PD, Parkinson's disease; PD-1, PD with short disease duration; PD-2, PD with long disease duration.

The two independent groups of PD patients differs in their average disease duration [2.11(PD-1) vs. 7.43(PD-2); see Table 1] and were defined as short versus long disease duration, respectively, based on this significant statistical difference.

The datasets of healthy participants (HC-1 and HC-2) were derived from the Alzheimer's Disease Neuroimaging Initiative (ADNI; https://adni.loni.usc.edu/), which includes a healthy population of older adults. (The two groups were comparable in term of connectivity in the ToM network, both at network and at ROI-to-ROI level; see Figure S1.) ADNI is a multicentre longitudinal project aimed at establishing biomarkers for the early detection of Alzheimer's disease.

Participants were excluded for excessive (head movement >3 mm along one of the axes) head movements during scanning or due to excessive mean frame-to-frame displacement [mean (FD); identified as an outlier, presenting values greater than 3 scaled median absolute deviations from the median of the initial sample]. See Supporting Information for a comparison of head-motion parameters between groups (Table S1).

2.2 | ROI selection

For this study, we considered a recent neuroanatomical model of ToM (Abu-Akel & Shamay-Tsoory, 2011) and selected the following regions of interest for the three subnetworks from the Brainnetome Atlas (https://atlas.brainnetome.org/publications.html) (Fan et al., 2016):

1. *cToM*: dmPFC, dlPFC, dACC, dATL, caudate, putamen.
2. *aToM*: OFC, vmPFC, vACC, vATL, liFC, Amyg, accumbens.
3. *coreToM*: IPL (BA 39,40), pSTS and PreCun.

2.3 | Resting-state functional connectivity analysis

We used the CONN toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012; available at https://www.nitrc.org/projects/conn) for resting-state connectivity (rs-connectivity) analyses. We followed a standard preprocessing pipeline: all images were slice-time corrected, realigned to correct for head movement, normalized to MNI space. We also included outlier detection (ART-based identification of scans for scrubbing) and bandpass filtering (0.01–0.1 Hz). We used white-matter and CSF time series as regressors of no interest (CompCor function for denoising steps). The six head-motion parameters were also included as additional regressors of no interest. ROI-to-ROI connectivity analysis was computed (Fisher's z-transformed pairwise Pearson's correlation coefficients, retaining both positive and negative values), obtaining a symmetric matrix of connectivity values for each participant. See Supporting Information for a visual representation of raw connectivity values in the ToM network of our experimental groups (Figure S2).

2.4 | Statistical analyses

We directly compared the connectivity pattern of PD-1 versus HC-1, PD-1 versus PD-2 and PD-2 versus HC-2. We considered the ROI-to-ROI connections following two approaches: (1) by adopting 'network overall degree of connectivity' (a sum of connectivity values) as a summary measure of connectivity within and between the cToM, aToM and coreToM subnetworks and (2) by directly comparing the ROI-to-ROI connectivity values within all regions of the three subnetworks.

In order to consider the possible role of sex in capturing connectivity differences between experimental groups, we compared the connectivity pattern between groups using an ANOVA with *Group* and *Sex* as independent variables and *connectivity* as dependent variable [correcting for multiple comparisons through false discovery rate (FDR), $q < 0.05$]. All the reported results are FDR-corrected, except where otherwise specified. To enhance the readability of our results, we examined the ROI-to-ROI connectivity differences separately within each hemisphere (right, left) and between hemispheres (right/left).

The significant values reported in the text and in the figures refer to the main effect of Group in the ANOVA (our effect of interest). The interaction term, indicating an effect of sex on group differences, is highlighted in Figure 1 and reported in the text, accordingly. Although it was not within the objectives of the present study, we added figures representing the main effect of Sex in the Supporting Information (Figures S3 and S4).

Given that our two PD samples differed on the general cognitive state (indexed by MoCA scores; see Table 1), we run a post hoc analysis to investigate whether the connectivity difference between groups was also influenced by general CI. Accordingly, we run an ANCOVA on connectivity, defining *Group* as between-subjects factor and using *MoCA score* as predictor of no interest. This post hoc analysis involved a subsample of the original cohort of PD patients, given that we had data related to MoCA score only for 54 subjects of PD-1 and 21 of PD-2.

3 | RESULTS

3.1 | Differences in overall degree of connectivity within the ToM network

Looking at the results of the network overall degree of connectivity (Figure S5), all four groups showed a similar pattern of positive connectivity within and between ToM subnetworks. From a qualitative point of view, average connectivity within the Core ToM seemed to be consistently greater in each hemisphere. Between-hemisphere connectivity of homologous regions was generally greater than within-hemisphere connectivity (see Figure S5).

3.1.1 | PD-1 vs. HC-1

When comparing PD-1 ($n = 72$) and HC-1 ($n = 69$), we observed a significant difference within the cToM (right: $p = 0.003$; left: $p = 0.005$), between the cToM and aToM (right: $p < 0.001$; left: $p < 0.001$) and between the core-ToM and the cToM (right: $p = 0.007$; left: $p = 0.006$) in both hemispheres, and within the aToM in the left hemisphere ($p = 0.008$) (Figure 1a). When considering cross-hemisphere connections (Figure 1a), we saw a significant difference, mainly between networks, and in particular, between right cToM and left aToM ($p = 0.005$), between right aToM and left cToM ($p < 0.001$) and between right CoreToM and left cToM ($p = 0.01$). Significant differences were due to higher connectivity strength in HC-1 (see Figure S5a,b).

3.1.2 | PD-2 versus PD-1

To investigate functional alterations of the ToM network across time in PD, we included an independent sample of PD (PD-2) of similar disease stage (average Hoen and Yahr stage <2) compared to the main PD-1, but of longer and more heterogeneous disease duration (see Table 1).

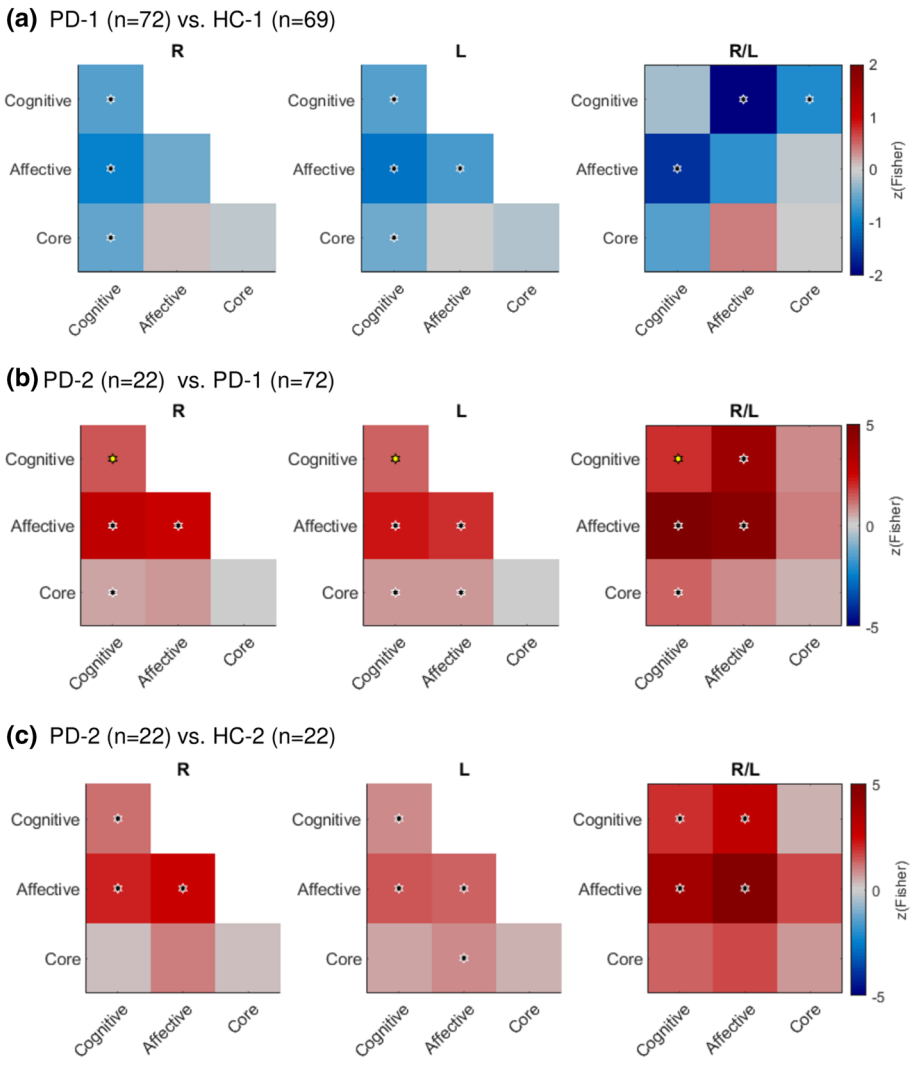

FIGURE 1 Differences in overall degree of connectivity in the ToM network. Overall degree of connectivity (sum of connectivity values) differences within and between the three ToM subnetworks—namely, Cognitive, Affective and Core ToM—are presented for each group comparison. (a) Difference between PD-1 ($n = 72$) and HC-1 ($n = 69$). (b) Difference between PD-2 ($n = 22$) and PD-1 ($n = 72$). (c) Difference between PD-2 ($n = 22$) and HC-2 ($n = 22$). In each differential matrix, values represent mean network difference in overall degree of connectivity (Fisher's z score); red represents positive differences, and blue, negative differences. Black stars represent significant results (main effect of Group), FDR corrected ($q < 0.05$). Yellow stars represent a significant interaction effect between factors Group and Sex FDR corrected ($q < 0.05$).

Overall, PD-1—with shorter disease duration—showed a lower level of connectivity within the ToM network, compared to PD-2, with longer disease duration (Figure 1b). In particular, we observed a significant difference within the cToM (right: $p < 0.001$; left: $p < 0.001$), within the aToM (right: $p < 0.001$; left: $p < 0.001$), between the cToM and aToM (right: $p < 0.001$; left: $p < 0.001$) and between the cToM and the CoreToM (right: $p = 0.038$; left: $p = 0.007$) in both hemispheres. In the left hemisphere, also connectivity differences between the aToM and the CoreToM were significant ($p = 0.009$). Looking at the between-hemisphere connections, results showed a significant difference within the cToM ($p < 0.001$); within the aToM ($p < 0.001$); between the right cToM and left aToM ($p < 0.001$), between the right aToM and left cToM ($p = 0.009$) and between the right cToM and left CoreToM ($p = 0.009$).

Notably, a significant effect of interaction involving the sex grouping factor (*Group* × *Sex*) was present within the cToM within the right and left hemisphere separately and between the nodes of the cToM across hemispheres (see yellow stars in Figure 1).

3.1.3 | PD-2 versus HC-2

To explore the functional alterations in the PD-2 group, we selected an independent and comparable sample of healthy controls (HC-2) in terms of age and sample size. Overall, similarly to the comparison with the short-duration group (PD-1), the PD-2 group showed increased connectivity within the ToM network (Figure 1c). Specifically, we saw a significant group difference within the aToM (right, $p < 0.001$; left, $p = 0.007$), within the cToM (right, $p = 0.008$; left, $p = 0.023$) and between the cToM and aToM (right, $p < 0.001$; left, $p < 0.001$) in both hemispheres and between the aToM and the CoreToM in the left hemisphere ($p = 0.023$). Significant group differences in the connections between hemispheres were present between right and left aToM ($p < 0.001$), between right and left cToM ($p = 0.033$), between right aToM and left cToM ($p = 0.0046$) and between left aToM and right cToM ($p < 0.001$).

Post hoc analysis regarding the general cognitive status of the PD patients suggests that the majority of the differential connectivity effects between the two groups of PD were not influences by levels of CI. Only in the right hemisphere, we found a significant interaction between *Group* and *MoCA scores* in the connections within the aToM ($p = 0.0023$) and between CoreToM and aToM ($p = 0.0122$) (Figure S6).

3.2 | ROI-to-ROI connectivity differences within the ToM network

Looking at the ROI-to-ROI connectivity values (Figure S7), there is a general trend for positive connectivity in the ToM network. However, several exceptions are present in the pairwise ROI-to-ROI connections, with distinct negative connections, particularly in the PD-1, the short-disease-duration group (see Figure S7).

3.2.1 | PD-1 versus HC-1

Significant differences were particularly present within the cToM, between the cToM and aToM and between the coreToM regions and the cToM—in both hemispheres (Figure 2a). Overall, significant differences between groups were due to lower connectivity values in PD-1 (see Figure S7). In particular, the connections within the cToM regions and between the cToM and the aToM appeared to be almost unaltered within the two hemispheres (Figure 2a). Within each hemisphere, dmPFC, dlPFC and caudate were involved in several connectivity differences between groups. PD-1 showed significantly higher connectivity than HC-1 in between-hemisphere connections involving the dmPFC and dlPFC. The same regions presented higher connectivity within each hemisphere separately.

3.2.2 | PD-1 versus PD-2

There was a widespread difference between groups, both within and between the different subnetworks of the ToM (Figure 2b). Interestingly, the connections involving the coreToM regions seem to be the least different between the two groups of PD. The significant differences predominantly highlight an increased connectivity in the long-disease-duration group compared to the short-disease-duration group (Figure 2b). Considering the connections within each hemisphere, caudate, dmPFC, dlPFC, iFC, vmPFC and v/dATL were particularly involved in significant differences. In the right hemisphere, Amyg, OFC and accumbens were associated with differential connectivity between groups.

3.2.3 | PD-2 versus HC-2 (Figure 2c)

Group differences were less widespread than in the preceding comparisons. Significant differences arose mainly in the right hemisphere, with significantly different

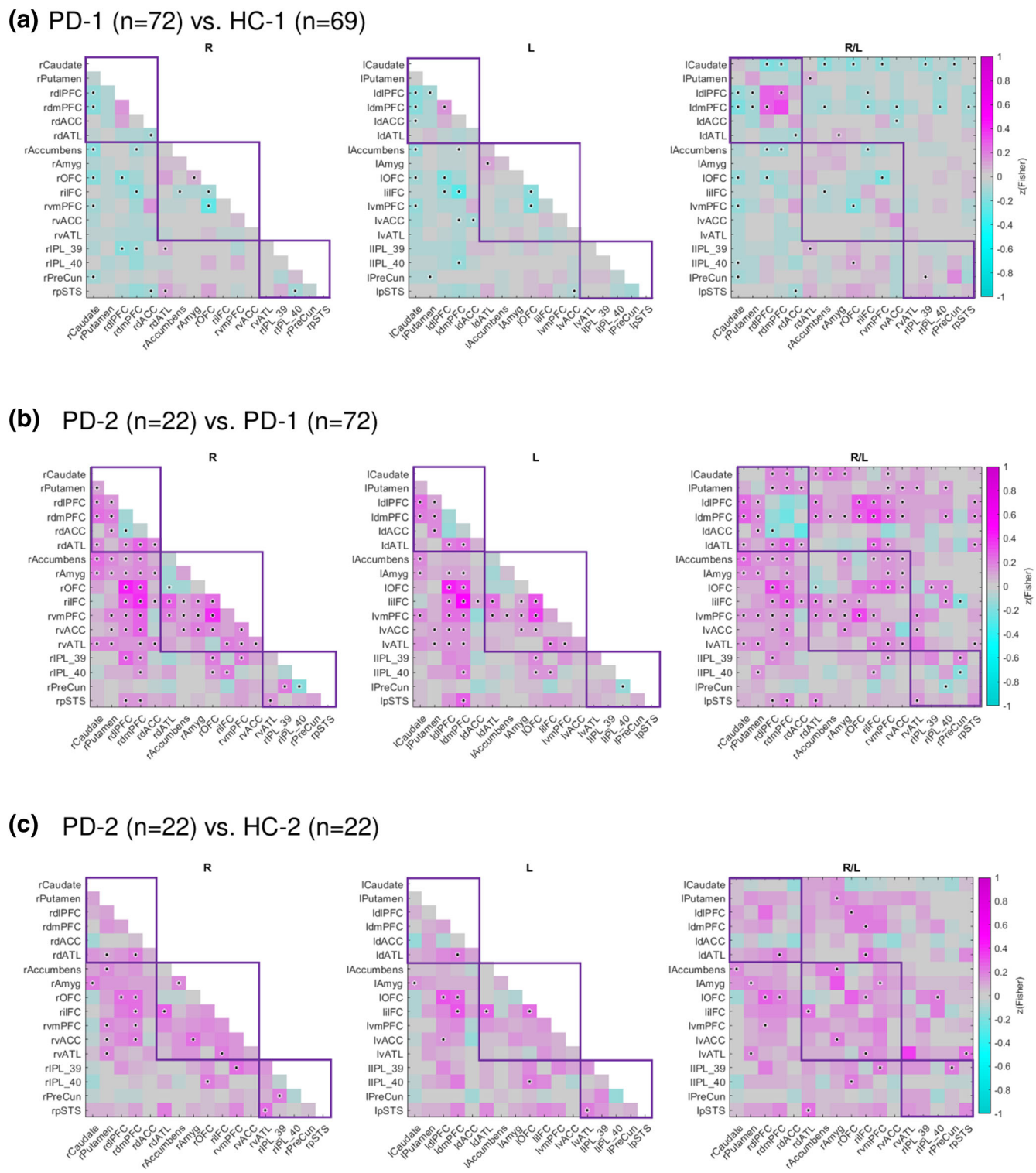

FIGURE 2 ROI-to-ROI connectivity differences in the ToM network. ROI-to-ROI connectivity differences within and between each region of the ToM network are presented for each group comparison. (a) Difference between PD-1 ($n = 72$) and HC-1 ($n = 69$). (b) Difference between PD-2 ($n = 22$) and PD-1 ($n = 72$). (c) Difference between PD-2 ($n = 22$) and HC-2 ($n = 22$). In each differential matrix, values represent raw connectivity difference (Fisher's z score); red represents positive differences, and blue, negative differences. Black stars represent significant results, FDR corrected ($p < 0.05$).

connections involving OFc, vmPFC, dlPFC, dmPFC and putamen. In the left hemisphere, regions particularly involved in significant differences were OFC, in relation to PFC and IPL, and iFC. In between-hemisphere connections, ROI-to-ROI connectivity differences were heavily present within the aToM and in the between-network connections, again engaging regions such as OFC, iFC, Amyg and putamen.

We did not report any significant effect of interaction between group and sex at ROI-to-ROI level.

There were only few regions showing a main effects of Sex (see Figure S4).

Furthermore, at ROI-to-ROI level, we did not report any significant effect of global cognitive status in the reported differences between the two populations of PD.

We conducted a further exploratory analysis (*conjunction analysis*) to identify the common ROI-to-ROI connections altered in all 'contrasts' involving PD groups, which we can summarize as (PD-1 vs. HC-1) and (PD-2 vs. PD-1) and (PD-2 vs. HC-2). Results showed that common altered connectivity was present in the right hemisphere between dmPFC and iFC and between OFC and dlPFC. In the left hemisphere, altered connectivity was present between dmPFC and iFC, between OFC and dlPFC and between OFC and iFC. In the between-hemisphere connections, common altered connections were present only between lOFC and rdlPFC (see Figure 3).

4 | DISCUSSION

Our study characterized the rs-connectivity profile of the ToM network in PD, revealing two novel insights into its functional organization. First, PD cohort present with functional alterations in rs-connectivity in the ToM network compared to HC, and particularly in its Cognitive and Affective subnetworks. Second, disease duration affects the connectivity profile of the ToM network: Compared to HC, PD showed decreased connectivity in early phases of the disease and increased connectivity with longer disease duration.

The ability to understand and predict thoughts, intentions and emotions of others is a fundamental prerequisite of effective social interactions. Not surprisingly, impairment of ToM is strictly related to perceived health-related quality of life (Bodden, Mollenhauer, et al., 2010) in PD. In recent decades, evidence has mounted of a general deficit in social cognition in PD (Alonso-Recio et al., 2021; Foley et al., 2019; Romosan et al., 2019; Yu et al., 2012). The few studies investigating the relation between brain function and ToM in PD focused mainly on the anatomical modifications associated with behavioural measures of ToM (Díez-Cirarda et al., 2015; Orso et al., 2020; Péron et al., 2010; Trompeta et al., 2021). Still, it is not clear whether the brain network classically involved in ToM also presents some degree of functional alteration in PD, regardless of the behavioural manifestation of ToM impairment.

We have shown that the ToM network in PD, as well as in HC, is characterized mainly by positive connectivity within and between the Cognitive, Affective and Core ToM subnetworks (Abu-Akel & Shamay-Tsoory, 2011). Overall, our finding of a global positive connectivity within the ToM network is not surprising, as the ToM network involves almost all the key nodes of the Default Mode Network (DMN), that is, precuneus, MFC and the inferior parietal cortex (Alves et al., 2019; Raichle, 2015; Smallwood et al., 2021). In this sense, the ToM network

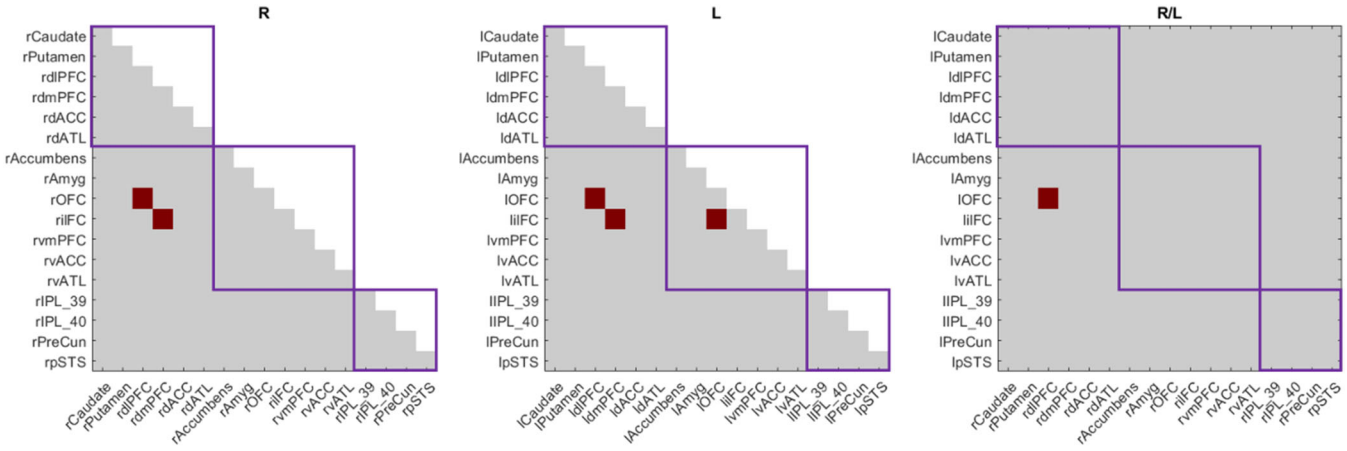

FIGURE 3 Conjunction analysis—common connections between-group differences. Results of the 'conjunction analysis' showing the common ROI-to-ROI connections altered in all the contrasts involving the PD-1 group. Red squares represent the connections that were altered in all contrasts run: (PD-1 vs. HC-1) and (PD-2 vs. PD-1) and (PD-2 vs. HC-2).

presents at least a partial overlap with the DMN (Mars et al., 2012). The DMN is thought to be involved in self-referential processing, internal focusing and reflection on own emotional states (Buckner & DiNicola, 2019; Yeshurun et al., 2021). All these functions are perfectly comparable with ToM processes, highlighting a strict relation between the connectivity patterns of these two networks at rest (Mars et al., 2012).

Interestingly, we saw that PD presented an altered pattern of functional connectivity within the ToM network when compared to HC. The PD-1 group (short disease duration) showed widespread decreased connectivity, encompassing the connections within the cToM, between the cToM and aToM and between the CoreToM and cToM—in both hemispheres. In the left hemisphere, we also saw significant differences within the aToM. The alteration of both the Cognitive and the Affective subnetworks of ToM seems to suggest a widespread alteration of the network, although the Cognitive portion seems to be affected more consistently. Despite the absence of behavioural measures of ToM in the present study, the results at brain level appear to be in line with a concomitant impairment of Cognitive and Affective ToM (and their reciprocal connections) in the early stages of PD (Maggi et al., 2022; Santangelo et al., 2012). Functional connectivity changes in PD have been frequently described (Cerasa et al., 2016), yet mainly focusing on the sensorimotor network (Caspers et al., 2021; Tessitore et al., 2014). Our results are in line with the recent proposal of an initial widespread hypoconnectivity in PD (Filippi et al., 2021) and resonates with the description of decreased connectivity within the DMN in cognitively unimpaired PD (Tessitore et al., 2012). Here, we report that the disruption of the DMN in cognitive unimpaired patients extends to the ToM network at large. Regions like caudate, dlPFC and dmPFC seem particularly involved in the differential connectivity pattern between PD and HC, which instead is compatible with the general fronto-striatal alteration detectable in PD (Cerasa et al., 2016).

Starting from the description of an early hypoconnectivity in TOM networks in early stages of PD, we explored whether disease duration might have an impact on the connectivity pattern of the ToM networks.

By comparing two independent PD groups with different disease durations, we painted a more comprehensive picture, as increased connectivity characterizes the ToM network of PD with long disease duration. This effect encompasses the Cognitive and Affective ToM subnetworks and their reciprocal interactions—in both hemispheres. Increased connectivity in PD has already been reported, in particular within the striatal-motor circuitry (Baudrexel et al., 2011; Tessitore et al., 2019; Yang et al., 2016). Here, we showed that a similar pattern is present in the ToM network. The neuroscientific outcome of increased connectivity in these patients still needs to be elucidated. Higher connectivity within the motor network—or between the cerebellum and the sensorimotor network—has been interpreted as a compensative effect opposing pathological PD brain alterations (Tuovinen et al., 2018), though it has frequently been associated with behavioural deficits (Herz et al., 2016; Tuovinen et al., 2018). Here, we show that increased disease duration is accompanied by an overall increase in functional connectivity within the ToM network. Still, it was not possible to clarify the relationship between behavioural deficits and the neural alterations we measured, as no ToM-specific behavioural measures were available.

Moreover, the dopaminergic deficit in PD is usually countered with the use of levodopa-based treatments, which should produce a normalization effect on decreased connectivity in the PD brain, especially between the striatum and the motor and the attentional networks (Kelly et al., 2009). This has also been shown in the DMN (Krajcovicova et al., 2012; Zhong et al., 2019). In this regard, given that our samples were tested in a medication-ON state, it is possible that the global increase in connectivity in the ToM network could be at least partially attributable to a prolonged exposure to levodopa treatment. On the other hand, given the evidence of an earlier dopamine depletion in the dorsal striatum compared to the ventral striatum (MacDonald & Monchi, 2011), it would also be reasonable to hypothesize a more critical effect of levodopa treatments in early stages of the disease, primarily in the networks and functions mediated by the dorsal striatum. Our results point instead to a general increase in connectivity in the ToM network in the PD population with longer disease duration.

It is worth noting that the connectivity profile in the Core ToM remains almost unaltered, suggesting that the functional connectivity among this set of regions (precuneus, pSTS, IPL) remains stable throughout disease duration. Those regions are thought to constitute the gateway of ToM processing, allowing the discriminability of agency, and they function as a relay for internal versus external focusing of attention (Abu-Akel & Shamay-Tsoory, 2011). Our results point to an alteration of connectivity involving the domain-specific systems (those of the Affective and Cognitive subnetworks), instead of the domain-general areas (those of the Core ToM). This latter observation is further reinforced by the results highlighting common altered connections between both the comparison of PD-1 with HC-1 and that of PD-1 with PD-2. This altered connectivity consists mainly of connections between cToM and aToM, involving regions like OFC and dmPFC and iFC. Those regions are pivotal in the ToM

network (Abu-Akel & Shamay-Tsoory, 2011) and belong to both the Cognitive and Affective subnetworks of ToM.

Notably, we reported limited effect of sex and global CI in the group differences highlighted in our main analyses (mainly involving the cognitive ToM subnetwork for sex and the affective for MoCA scores). To some extent, our results are compatible with previous literature showing connectivity differences related to sex (Smith et al., 2014; Weis et al., 2020) and global CI (Fiorenzato et al., 2019; Hassan et al., 2017; Lucas-Jiménez et al., 2016). In this sense, future investigations might take into consideration those variables as confounding factors when comparing different groups of PD or when comparing healthy controls with patients as well. On the other hand, the limited effects we found suggest that, at least in the brain networks involved in ToM, these confounding variables play a limited role in the differences shown between our experimental groups, stressing further the effects of the pathology and disease duration on functional alterations related to theory of mind in PD.

5 | CONCLUSIONS

Along with other higher-order cognitive functions, social cognition is also impaired in PD (Strikwerda-Brown et al., 2019), and it begins at an early stage of the disease (Dodich et al., 2022; Mattavelli et al., 2021). The development of novel prevention strategies demands a substantial effort to understand the brain correlates of these social cognition deficits.

Here we focused on ToM in PD, showing substantial functional connectivity alterations among PD with short disease duration, healthy controls and PD with long disease duration. We showed a graded pattern, consisting of a generally decreased connectivity in the early years of disease (PD short disease duration) compared to healthy controls, which progresses to an overall aberrant connectivity increase in PD with longer disease duration. These widespread functional alterations occur in both the Affective and Cognitive subnetworks of ToM.

6 | LIMITATIONS AND FUTURE DIRECTIONS

We acknowledge that our study presents several limitations. The lack of behavioural measures of ToM in our samples preclude linking our rs-connectivity modifications with possible behavioural impairments. Future investigations should try to relate the connectivity profile of the ToM network with the manifestation of ToM-related deficits.

The group comparisons are potentially confounded by different acquisition protocols in the rs-fMRI sessions. The comparison between the two PD groups is confounded by differences in sample size and level of global cognition. Again, this gap might be addressed in future studies.

We did not consider the laterality of the symptoms at disease onset, which could have affected the results we reported in the two hemispheres. Whether the side predominantly affected at onset could have an impact on the distribution of altered connectivity across hemispheres in PD is another question for future investigations. Finally, we intentionally focused on the ToM network as defined by previous authors (Abu-Akel & Shamay-Tsoory, 2011). However, a comprehensive investigation into the relation between resting state connectivity and ToM deficit could extend to whole-brain analyses. Accordingly, the seed-based approach might highlight the roles of pivotal regions of the ToM network in the behavioural manifestation of the impairment.

AUTHOR CONTRIBUTIONS

Giuseppe Rabini and Luca Turella conceived and designed the study. Giuseppe Rabini performed the analyses and wrote a first draft of the manuscript. Giuseppe Rabini, Luca Turella, Alessandra Dodich and Costanza Papagno reviewed the first version of the manuscript. All authors reviewed the final version of the paper.

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CONFLICT OF INTEREST STATEMENT

The authors report no competing interests.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data that support the findings of this study are available at (1) the PPMI-database online (www.ppmi-info.org/access-data-specimens/download-data), upon specific request to the PPMI committee (PD-1 group); (2) the

ADNI-database online (https://adni.loni.usc.edu/data-samples/access-data/) upon specific request to the ADNI committee (HC-1 and HC-2 groups); and (3) from the corresponding author upon reasonable request (PD-2 group). Analysis scripts are available upon specific request to the authors.

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SUPPORTING INFORMATION

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