Review

Theory of Mind in Parkinson's disease

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A B S T R A C T

The ability to infer other people’s mental states (i.e. Theory of Mind, ToM) is a major topic of interest in various neurological and psychiatric disorders. However, it is only recently that there has been an assessment of cognitive and affective components of ToM ability in neurodegenerative disorders. In this review, we examine studies investigating the ToM ability in Parkinson’s disease (PD). Taken together, these studies provide preliminary evidence that ToM difficulties may occur in PD patients. In particular, these difficulties principally involve the cognitive component of ToM in the early stages of the disease. The spatio-temporal progression of dopamine depletion supports the hypothesis that the affective component may only be affected in the advanced stages of the disease. The relationships between executive functioning, dopaminergic therapies, and ToM in PD as well as the relationships between frontostriatal circuits and ToM processing are discussed.

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1. Introduction

Parkinson's disease (PD) is a common neurodegenerative condition clinically defined by motor symptoms including bradykinesia, rigidity, resting tremor, and postural instability. Non-motor symptoms such as cognitive impairment and neuropsychiatric disturbances can also be present. These symptoms can be just as disabling as motor dysfunctions [30]. Mild cognitive impairments are usually present from the untreated and the early-medicated stages of PD, affecting about 20–30% of patients, with deficits being most prominent in the domains of memory, executive functions,
2. Prefrontal functioning in Parkinson’s disease

PD is primarily caused by a loss of dopaminergic neurons in the nigrostriatal tract, producing a reduction in dopamine levels in the striatum. This dopamine depletion impacts the functioning of four frontostriatal circuits involved in different motor, cognitive, affective, and motivational aspects of behavior [5,22,50,70]. Three of these circuits are of particular interest for the study of cognitive and ToM dysfunctions in PD patients (see Fig. 1): the dorsolateral circuit, including the dorsolateral prefrontal cortex (DLPFC), the striatum (dorsolateral caudate nucleus), the globus pallidus (dorsomedial), and the thalamus; the orbital circuit, including the orbitofrontal cortex (OFC), the striatum (ventromedial caudate nucleus), the globus pallidus (dorsomedial), and the thalamus; and the ventral striatum, including the nucleus accumbens, the olfactory tubercle, the globus pallidus (rostromedial), and the thalamus [17].

Within each circuit, two loops connect the striatum with the prefrontal cortex (PFC): a direct excitatory loop and an indirect inhibitory loop [5,40,47]. In the early stages of the disease, the dysexecutive syndrome (impairment of attention and of executive functions), which affects most PD patients, is principally due to a reduced dopaminergic stimulation at the striatal level, which progressively disrupts the normal functioning of the frontostriatal circuits [58,76]. As a matter of fact, recent anatomical and neuropathological evidence suggested that the evolving pattern of executive impairment in PD might be explained in terms of what is known about the spatio-temporal progression of dopamine depletion within the striatum. In the early stages of PD, dopamine depletion is the greatest (maximum, 90%) in the most dorsolateral portion of the head of the caudate nucleus, an area involved in the dorsolateral frontostriatal circuit described above [64]. In the early stages of PD, the cognitive processes based on this dorsolateral frontostriatal circuit, which provide a cognitive control of information and actions [9] are usually impaired, whereas the processes based on the orbital frontostriatal circuit, which provide an automatic reward-based control of information and actions [9,105] are almost preserved. With the progression of PD in the later stages of the disease, in which the PFC is directly affected by the neuropathology [91], the dopamine depletion within the striatum also affects the orbital frontostriatal circuit producing an impairment of related functions [33,89].

The spatio-temporal difference in dopamine depletion at the striatal level explains why the administration of L-dopa is not linearly correlated to cognition. An inverted U-shaped curve better describes the relationship between dopamine and cognitive functions, as demonstrated by a series of studies [34–36,38], for a review see [33]. The withdrawal of dopaminergic medication in patients with early PD has a detrimental effect on task-set switching, which is associated with the dorsolateral frontostriatal circuit, while having a beneficial effect on probabilistic rever-
The ability to recognize, manipulate, and behave with respect to socially relevant information requires neural systems that process perception of social signals and connect such perception to motivation, emotion, and adaptive behavior [3]. Social cognition guides both automatic and volitional behavior, being composed of a variety of cognitive, emotional, and motivational processes that modulate behavioral responses: memory, decision-making, attention, motivation, and emotion are all prominently recruited when socially relevant stimuli elicit behavior [4].

Functional neuroimaging has revealed that processing of social information activates complex neural networks that include cortical and subcortical structures, those involved in the emotional elaboration of stimuli, such as the amygdala, and those involved in the cognitive elaboration of stimuli, such as the temporoparietal junctions (TPJ) and the medial prefrontal cortex (MPFC) [100]. Perception, elaboration, and reaction to social stimuli actually require a continuous interaction of cognitive and emotive processes [75]. Examples of abilities referable to the domain of social cognition are both the capacity to represent other people's intentions and beliefs, and the capacity to recognize and share the emotions and sensations of others (empathy) [67]. Although in literature the use of the terms ‘ToM’ and ‘empathy’ is occasionally unclear and mixed, recently Singer [95] clearly showed that ToM and empathy display different ontogenetic trajectories reflecting the different developmental pathways of their distinct underlying neural structures. As far as these abilities are concerned, the present paper focuses on the ToM ability.

Findings from neuroimaging [11,25,32,43,48,90,101] and lesion studies [92–94,96,97] support the possibility of linking the ability to represent other people’s mental states, i.e., ToM ability, with its neural underpinnings. These studies have demonstrated the critical role of specific brain regions in the key social ability of ToM: the PFC (specially its medial portions), the temporal poles, the pSTS, and the neighboring but distinct region of the TPJ. Furthermore, it is worth noticing that the ACC, a crucial area in the anterior cingulate cortex, is selectively disrupted: whereas the ventromedial prefrontal cortex has an important role in processing affective ToM [92], the DLPCF is involved in cognitive ToM [60]. Consequently, recent studies revealed how ToM subcomponents are differently linked to the frontostriatal circuits affected in PD: while the affective ToM is thought to be mediated predominantly by the orbital frontostriatal circuit, the cognitive ToM might additionally be related to the dorsolateral frontostriatal circuit [20,21].

Two different theoretical perspectives have been hypothesized to explain the different ToM subcomponent processes. According to the ‘simulation theory’ perspective, others’ mental states are modelled via a simulation routine, where attributors use their own mental states to predict the mental processes of others [49]. On the other hand, ‘theory theory’ posits that others’ mental states are modelled rationally by a knowledge system that is independent from one’s own mental states [52]. As recently suggested by Kalbe et al. [59] and by Shamay-Tsoory et al. [92,94], the cognitive subcomponent of ToM may primarily involve a set of cognitive processes which relies on rational ‘theories’ of the mind corresponding to the ‘theory theory’ perspective, whereas the affective subcomponent of ToM may be mainly explained by the simulation perspective.

The five ToM tasks mostly employed in both neuroimaging and lesion studies and in PD studies are the first- and second-order false belief test (two tasks which evaluate the cognitive component of ToM), the Reading the Mind in the Eyes (RME) test (evaluating the affective component of ToM), the Faux Pas Recognition test (FPR), and the Yoni test (tasks involving aspects of both affective and cognitive ToM). Because of the crucial role played by these tests in the studies assessing ToM ability in PD, we will briefly describe each of them, and the kinds of experimental tasks that participants are invited to complete.

The first-order false belief test is a classical task designed to assess an individual’s ability to infer that someone has a mistaken belief about the world (e.g. A’s beliefs about the location of an object) that is different from the individual’s own true belief [15,104]. The second-order false belief test [12,80] is more complex than the first-order test since in this situation it is not sufficient to infer another person’s thoughts about the world, but it is crucial to form beliefs about the content of that person’s mind (e.g. B’s beliefs about A’s beliefs about the location of an object). Both first- and second-order tests are traditionally used to assess the cognitive component of ToM.

The RME test is an advanced affective ToM task consisting of the presentation of photographs of the eye region of human faces [14,16]. Participants are required to choose which word best describes what the individual in the photograph is thinking or feeling (e.g. which of the following words best describes the eye region shown: excited, relieved, shy, or despondent). In the FPR test, the participant hears ten stories read aloud containing a social faux pas, and ten control stories reporting a minor conflict, but in which no faux pas is committed [96]. After each story, participants are asked whether anyone said anything that they should not have said, i.e., to correctly identify the stories containing a faux pas. When a faux pas is detected, further clarifying questions are proposed in order to evaluate the participant’s understanding of the situation (e.g. a cognitive component: why do you think the character said it? and an affective component: how do you think the character felt?). Thus, FPR was designed to differentially assess both the cognitive and affective aspects of ToM. Finally, in the Yoni test [60,92], a face named ‘Yoni’ is shown, in the middle of a computer screen, with four coloured pictures in the corners showing either faces and/or examples of a semantic category (e.g. animals, fruits). Participants have to evaluate which of these four pictures best corresponds to a sentence contemporaneously presented on each screen about
which image Yoni is referencing. The items can be subdivided into three types of categories that correspond to affective ToM, cognitive ToM, and control conditions. While answers for the control condition only require an analysis of the character’s physical attributes, choices in the affective and cognitive ToM items imply mentalizing based on verbal cues contained in the sentences, eye gaze, and/or facial expression (e.g. cognitive component: Yoni is thinking of . . . , affective component: Yoni loves . . . , and control condition: Yoni is close to . . .). Items differ in complexity with both first-order and second-order items included.

In adult subjects, the performance in tasks based on the implicit ability to infer the feelings of another person observing their eyes only (RME test), faces or pictures (affective component of the Yoni test), or based on the ability to detect faux pas in social situations (FPR test) is impaired when the ventromedial prefrontal cortex is damaged [92,93], specially in the right hemisphere [94]. The performance in tasks based on the ability to infer others’ beliefs (first- and second-order false belief tests or the cognitive component of the Yoni test) is impaired when the prefrontal damage is extensive, also affecting more lateral portions [92].

4. Theory of Mind processing in Parkinson’s disease

The previously described ToM tasks, the different role played by the PFC in those tasks, and the connections of the PFC with other neural structures involved in PD can be used as the starting point to describe and summarize the findings of the ten studies that have assessed ToM processes in PD patients (see Table 1).

4.1. Reading the Mind in the Eyes test and Parkinson’s disease

Six studies adopted the RME test in patients with PD. The majority of those studies suggested that the performance of medicated PD patients in the RME test may be preserved in the early [44,71,86] and advanced stages of the disease [81,82].

Besides the PD patients evaluated by Peron et al. [81] after deep brain stimulation (DBS), only the study by Bodden et al. [21] reported lower RME performances of medicated PD patients compared to those of healthy controls. However, the mean performance of PD patients in the latter study (51.7% of mental states appropriately rated) was similar to that of 53.4% reported in the study by Euteneur and colleagues [44], in which PD patients and healthy controls performed similarly. Moreover, in the study by Bodden et al. [21] healthy controls were younger than PD patients (mean age, respectively 58.7 years and 63.7 years), even if the difference was not statistically significant (p = 0.10). The mean age of the controls is particularly important considering that the RME performances are reported as declining with age in healthy subjects [78]. This suggests that the selection of the healthy control sample may have influenced the comparison with PD patients in the study by Bodden et al., in particular for the RME test. In another study [71], the medicated PD patients obtained poorer scores than the healthy controls, but the authors highlighted that the performances on the RME test by both the PD and control subjects were relatively high, although not ceiling.

It is worth noting that in the only study [82] where early PD patients were tested both ‘on’ and ‘off’ dopaminergic therapy, no differences were found in RME performances between the controls, early PD patients (both ‘on’ and ‘off’ dopaminergic therapy), and advanced PD patients. However, the authors suggested that the double test, even if conducted with parallel versions of the RME test, could have induced a learning effect in the early PD patients’ sample. Interestingly, in a following study, Peron et al. [81] reported no differences in the RME test between PD patients in the pre-operative conditions and healthy controls, while PD patients in the post-operative conditions reported lower performances compared to the healthy controls. Post-operative performances of PD patients were significantly lower than pre-operative ones.

Finally, in the study by Roca et al. [86], the RME test was administered to both early-medicated PD patients and unmedicated de novo PD patients. It is important to note that this study is the only one involving unmedicated PD patients. No differences were found between medicated PD patients, unmedicated PD patients, and healthy controls. Considering the whole patient group, no correlations were found between ToM score and performances in executive tasks such as the Wisconsin Card Sorting Test.

4.2. Faux Pas Recognition test and Parkinson’s disease

Three studies assessed the detection of faux pas in social situations in PD patients and found convergent evidence showing a preserved performance to the affective component of the FPR test and an impaired performance to the cognitive component. In particular, Kawamura and Koyama [62] reported that patients with PD were as able as controls to detect the inappropriate remarks in the stories (the affective component of the task) but had more difficulties to infer the reason why the person in the story had made an inappropriate remark (the cognitive component of the task). Similar findings were reported by Peron et al. [82]. In their study the FPR test was administered, as previously mentioned, to early-medicated PD patients ‘on’ and ‘off’ medication and to advanced medicated PD patients. No differences were found in the emotion attribution score (the affective component of the task) between controls, early PD patients (‘on’ and ‘off’ dopaminergic therapy), and advanced PD patients. In terms of the cognitive component of the task (the intention attribution score), the early PD patients’ performance was similar to that of controls either ‘on’ and ‘off’ dopaminergic therapy, while advanced PD patients showed poorer performances compared to controls and ‘off’ medication early PD patients but not compared to ‘on’ medication early PD patients. Finally, in the study by Roca et al. [86], healthy controls outperformed medicated PD patients but not the unmedicated PD patients in the FPR total score. Considering the cognitive and affective components of the FPR test, healthy controls and PD patients, regardless of the medication, performed similarly on the affective component. However, a significant difference was found in the cognitive component: the healthy controls outperformed both the medicated and unmedicated PD patients, and no differences were found between the medicated and unmedicated PD patients. In this study, considering the whole patient group, no correlations were found between FPR total score and performances in executive tasks.

4.3. Others’ beliefs tests and Parkinson’s disease

The inference of others’ beliefs has been assessed in three studies. Monetta et al. [72] administered the first- and the second-order story tests and reported poorer performances in the PD patients compared to the healthy controls in the second-order story test. Another study [88] employed a wider set of ToM tasks together with the first- and second-order false belief tests: the perspective-taking test [29], in which patients were asked to predict what another person (who had not seen an entire picture) would think the picture was; the spy test [55], in which patients were asked to create a strategy to retrieve a secret document without getting caught; the deception test [84], in which patients had to detect deception in the examiner’s actions while trying to guess under which cup the examiner had hidden a paper clip. Compared to the age-matched healthy controls, the PD patients had poorer performances in the false belief tests and in the spy test and preserved performances in the perspective-taking test and the deception test. Considering that these tasks involve cognitive aspects of ToM, different levels
Table 1
PD studies including Theory of Mind tasks. The order is chronological.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sample</th>
<th>Patients’ mean age in years (SD)</th>
<th>Disease duration in years (SD)</th>
<th>LEDD/DRT in mg (SD)</th>
<th>Hoen and Yahr stage</th>
<th>MMSE (SD)</th>
<th>Task</th>
<th>ToM component</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saltzman et al., 2000</td>
<td>11 PD</td>
<td>71 (13.45)</td>
<td>N/A</td>
<td>N/A</td>
<td>2.5</td>
<td>Above 26</td>
<td>False beliefs</td>
<td>Cognitive</td>
<td>Impaired</td>
</tr>
<tr>
<td></td>
<td>8 HC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Spy task</td>
<td>Impaired</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Perspective taking</td>
<td>Cognitive</td>
<td>Preserved</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Deception task</td>
<td>Cognitive</td>
<td>Impaired</td>
</tr>
<tr>
<td>Mengelberg and Siegert, 2003</td>
<td>13 PD</td>
<td>72.9 (8.9)</td>
<td>5.4</td>
<td>N/A</td>
<td>4 II 6 III 2 IV</td>
<td>28.46 (1.39)</td>
<td>False Beliefs</td>
<td>Cognitive</td>
<td>Impaired</td>
</tr>
<tr>
<td></td>
<td>11 HC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Short Passage task</td>
<td>Cognitive</td>
<td>Preserved</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>First Order story</td>
<td>Cognitive and affective Component</td>
<td>Impaired cognitive component</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Second Order story</td>
<td>Cognitive</td>
<td>Impaired</td>
</tr>
<tr>
<td>Mimura et al., 2006</td>
<td>18 PD</td>
<td>68.9 (7.0)</td>
<td>N/A</td>
<td>N/A</td>
<td>II/III</td>
<td>27.8 (1.9)</td>
<td>False Beliefs</td>
<td>Affective</td>
<td>Slightly impaired</td>
</tr>
<tr>
<td></td>
<td>40 HC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Spy task</td>
<td>Cognitive and affective Component</td>
<td>Impaired cognitive component</td>
</tr>
<tr>
<td>Kawamura and Koyama, 2007</td>
<td>11 PD</td>
<td>67.1</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>28.1 (2.6)</td>
<td>Faux Pas Recognition</td>
<td>Cognitive</td>
<td>Impaired</td>
</tr>
<tr>
<td></td>
<td>20 HC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Reading the Mind in the Eyes</td>
<td>Affective</td>
<td>Preserved</td>
</tr>
<tr>
<td>Euteneuer et al., 2009</td>
<td>21 PD</td>
<td>67.6 (7.3)</td>
<td>7.1 (6)</td>
<td>487 (317)</td>
<td>2.5</td>
<td>29 (1.10)</td>
<td>Faux Pas Recognition</td>
<td>Affective</td>
<td>Preserved</td>
</tr>
<tr>
<td></td>
<td>23 HC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cognitive and affective</td>
<td>Cognitive and affective Component</td>
<td>Impaired cognitive component</td>
</tr>
<tr>
<td>Monetta et al., 2009</td>
<td>11 PD</td>
<td>67.1 (10.9)</td>
<td>9.1 (3.2)</td>
<td>N/A</td>
<td>2.5 (0.9)</td>
<td>140.3 (2.9) on MDRS</td>
<td>First Order story</td>
<td>Cognitive</td>
<td>Mostly preserved</td>
</tr>
<tr>
<td></td>
<td>11 HC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Second Order story</td>
<td>Cognitive</td>
<td>Impaired</td>
</tr>
<tr>
<td>Peron et al., 2009</td>
<td>17 early PD</td>
<td>61.0 (7.1)</td>
<td>2.5 (1.5)</td>
<td>458 (337)</td>
<td>On 1.0 (0.9)</td>
<td>Early PD On 138.8 (4.4)</td>
<td>Affective First Order</td>
<td>Impaired</td>
<td></td>
</tr>
<tr>
<td></td>
<td>26 HC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Early PD Off 140.4 (4.5)</td>
<td>Cognitive First Order</td>
<td>Preserved</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Advanced PD On 139.1 (4.1) on MDRS</td>
<td>Affective</td>
<td>Impaired</td>
</tr>
<tr>
<td>Bodden et al., 2010</td>
<td>21 PD</td>
<td>63.7 (10.0)</td>
<td>5.1 (2.8)</td>
<td>432.1 (316.8)</td>
<td>2.5 (Range 1.0–3.0)</td>
<td>29 (Range 28–30)</td>
<td>Affective</td>
<td>Impaired</td>
<td></td>
</tr>
<tr>
<td></td>
<td>21 HC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Reading the Mind in the Eyes</td>
<td>Cognitive</td>
<td>Impaired</td>
</tr>
<tr>
<td>Peron et al., 2010</td>
<td>13 PD</td>
<td>Pre-DBS 53.3 (8.5)</td>
<td>Pre-DBS 10.5 (3.6)</td>
<td>Pre-DBS 1081.1 (605)</td>
<td>Pre-DBS 1.9 (0.9)</td>
<td>Pre-DBS 141.4 (1.7) on MDRS</td>
<td>Affective First Order</td>
<td>Impaired</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13 HC</td>
<td>Post-DBS 625.8 (600)</td>
<td>Medicated 1.69 (1.55)</td>
<td>Post-DBS 1.2 (1.0)</td>
<td>Pre-DBS 141.1 (1.9) on MDRS</td>
<td>Cognitive First Order</td>
<td>Preserved</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medicated 317 (256)</td>
<td>Medicated1.42 (0.57)</td>
<td>Medicated 29.00 (1.55)</td>
<td>Post-DBS 141.1 (1.9)</td>
<td>Cognitive First Order</td>
<td>Preserved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roca et al. 2010</td>
<td>36 PD</td>
<td>Medicated 63.4 (8.47)</td>
<td>Drug-free 1.23 (1.56)</td>
<td>Drug free 1.33 (0.54)</td>
<td>Drug free 28.26 (1.45)</td>
<td>Drug free 28.26 (1.45)</td>
<td>Affective</td>
<td>Preserved</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(16 medicated 20 drug free) 35 HC</td>
<td>Drug free 63.5 (11.8)</td>
<td>Drug-free</td>
<td></td>
<td></td>
<td></td>
<td>Affective</td>
<td>Preserved</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Cognitive and affective</td>
<td>Cognitive and affective Component</td>
<td>Preserved cognitive component</td>
</tr>
</tbody>
</table>

DBS = Deep Brain Stimulation; DRT = Dopamine Replacement Therapy; FPR = Faux Pas Recognition; HC = Healthy Controls; LEDD = Levodopa Equivalent Daily Dose; MDRS = Mattis Dementia Rating Scale; MMSE = Mini Mental State Examination; N/A = Not Available; PD = Parkinson’s Disease; RME = Reading the Mind in the Eyes.
of performance by PD patients in these tasks may be due to their heterogeneity, with different non-ToM demands and loads.

Finally, in the study by Mengelberg and Siegert [69] PD patients performed a first-order story test, a second-order story test, a false belief test, and a short passage test. In the short passage test, patients were asked to make an inference about mental states or physical causation. PD patients had poorer performance compared to age-matched healthy controls in the false belief test, in the short passage test, and in the first-order story. However, their performance in the second-order story was preserved. These findings, i.e., an impaired first-order false belief inference and a preserved second-order false belief inference, may appear atypical: as a matter of fact, first-order false belief tests are easier than second-order false belief tests, the former being well performed from 3 to 4 years of age [104], and the latter from 6 to 7 years of age [12] by normally developing children. However, Mengelberg and Siegert [69] noted that there were a number of points worth mentioning in this regard. The first point is that on the second-order false belief test, PD patients performed at a lower level than healthy controls, even if the difference was not significant. Second, while not significant, at \( p = .09 \), the difference might be described as approaching significance, and a larger sample size might well have found a significant difference. The third point is that a floor effect was possibly operating in this task, making it difficult to detect a real difference between these groups; in other words, the task simply seemed too hard for both the PD patients and the healthy controls to demonstrate any difference in ToM ability between them.

4.4. Yoni test and Parkinson’s disease

The only one study adopting the Yoni test in PD patients [21] reported significantly lower performances, compared to healthy controls, in the second-order affective ToM component and in the second-order cognitive ToM component. It is worth noting that this is the only study that reported a clear impairment of affective ToM in medicated PD patients.

5. Discussion

Taken together, the findings we examined in the previous section can be summarized by suggesting that medicated PD patients may have preserved performance in affective ToM tasks, such as the RME test [44,71,81,82,86] and the affective component of the FPR test [62,82,86]; conversely, these patients may have difficulty performing cognitive ToM tasks such as the second-order false belief test [72,88], the cognitive components of the FPR test [62,82,86], and the Yoni test [21].

Only Bodden et al. [21] reported difficulties of affective ToM in medicated PD patients, as assessed by the RME test and the Yoni test. This finding needs further confirmation as it differs from empirical findings obtained with the RME and the FPR tests in all the other studies here reviewed. Moreover, Bodden et al. reported that performances in the RME test did not correlate with performances in the Yoni test, even if both tests are deemed to tap the affective component of ToM. As suggested by the authors, the missing relationship between the RME test and the Yoni test might be due to the fact that different aspects of affective ToM are required: in the RME test, the mental state of the depicted person has to be inferred by focusing the eye region only, while the Yoni test requires an integration of facial expression decoding and eye movement. Furthermore, while the RME test provides realistic material, the Yoni test comprises schematic material. In summation, considering (1) the slight difference in the mean age of samples (see Section 4.1), and (2) the lack of literature on the Yoni test and on its relationship with other ToM tasks, divergent findings by Bodden et al. [21], i.e., an impairment of affective ToM in PD patients, might be interpreted cautiously and need further confirmation.

The findings that emerged from the studies herein reviewed suggest that PD patients present with greater difficulties in tasks involving the cognitive component of ToM. From a neuropsychological perspective, these difficulties could be partially explained by the dysexecutive syndrome that may characterize PD patients from untreated and early-medicated stages of the disease [1,74]. As a matter of fact, although ToM and executive functions are proposed to be functionally independent [46,87], developmental studies [27,56] and studies on brain-damaged children [41] and adults [28] have shown that there is at least a correlation between performance levels in executive tasks – specially of working memory and inhibitory control – and ToM tasks. Even though the nature of the relationship between executive functioning and ToM remains a subject of debate [18], evidence from developmental studies on ToM suggests that working memory (as well as inhibitory control) is necessary to perform some cognitive tasks of ToM, such as false belief tests: for example, Moses et al. [73] suggest that children might fail a false belief test either because they lack the working memory capacity to hold in mind their own belief and the mistaken belief of the protagonist, or because they lack the inhibitory capacity to suppress the prepotent true state of affairs. Moreover, as suggested by Apperly et al. [8], in the current state of neuropsychological research there appears to be no definitive evidence for domain specificity of ToM, at least concerning the belief reasoning assessed with false belief tests. Accordingly, the relationship between working memory and ToM may explain why the false belief tests’ performance in brain-damaged subjects is impaired when the prefrontal damage is extensive, also affecting more lateral portions [92].

Working memory may play a crucial role in PD patients’ performance in ToM tasks as well, in particular concerning the impairment of dorsolateral executive functions. As previously discussed, in the early stages of PD the dopamine depletion affects the dorsolateral frontostriatal circuit [64] causing an impairment of related executive functions [33,74]. Although preliminary studies reported a preserved functioning of verbal working memory in PD patients in mild to moderate stages of PD [77], recent studies have detected impaired verbal working memory in the same population [26,42,51,65]. Specifically, the evidence that verbal working memory is affected in PD patients could partially explain why they have difficulty in the cognitive component of ToM tasks (false belief tests and the cognitive component of the FPR test) but not in the affective one (RME test and the affective component of the FPR test). Furthermore, the different working memory load of first-order false belief tests and second-order false belief tests could also explain the different performance levels of PD patients in these tasks (respectively preserved and impaired). A verbal working memory impairment associated with a set-shifting impairment was reported in the study by Monetta et al. [72], which showed PD patients to have ToM difficulties. Even though Roca et al. [86] did not find correlations between ToM and performance in executive tasks, other studies here discussed reported different results. Moreover, Saltzman et al. [88] reported executive difficulties of PD patients in fluency tasks and in a card sorting test; Peron et al. [82] found that advanced PD patients achieved lower performance levels than early PD patients in a verbal fluency task. In summation, the existence of an executive impairment could indirectly suggest that working memory was also affected in those patients. It is important to note, that even though working memory deficits could partially explain the difficulties encountered by the experimental subjects in the cognitive aspects of ToM tasks, other executive functions, such as cognitive flexibility, can directly affect performance on ToM tasks, and not just act as a proxy for working memory deficits [37].
As far as affective component of ToM is concerned, on the basis of the spatio-temporal progression of dopamine depletion within the striatum – and in relation to the terminal distribution of its cortical afferents – in later stages of PD, dopamine depletion also affects thosefrontostriatal circuits that connect the basal ganglia with more medial regions of the prefrontal cortex. This could suggest that the affective component of ToM may also be compromised in later stages of PD: however, only a study assessed the affective ToM component [82], with the RME test and the FPR test in early and advanced PD patients, reporting no significant differences between patients at different stages of the disease.

It is also important to consider that PD patients frequently present with asymmetric motor symptoms, suggesting that in the early phases of the disease the dopamine depletion often involves one hemisphere more than the other. The neuropsychological study of how dopamine asymmetries impact cognitive functioning is at an early stage and its findings are still controversial [39,61,99]. Considering dopamine asymmetries in PD and asymmetries in the neural correlates of some ToM processes, as shown by lesion studies (for example, the role of the right ventromedial prefrontal cortex in the detection of faux pas in social situations [94]), we suggest that future research should compare performances of different subgroups (left motor onset, right motor onset, bilateral motor onset) of PD patients in tasks of social cognition and ToM.

Regarding the influence of dopaminergic therapies on ToM processes in PD patients, only one study [82] assessed PD patients ‘on’ and ‘off’ dopaminergic therapy, reporting no differences in all the components (affective and cognitive) of ToM tasks. On the basis of these findings, the authors suggested that nigrostriatal and mesolimbic dopaminergic pathways do not contribute to ToM ability. Another study [86] did not find significant differences between medicated and unmedicated early PD patients in the RME test and the FPR test. However, no findings are available for performance levels of PD patients ‘on’ and ‘off’ dopaminergic therapy in cognitive ToM tasks only (false belief tasks). Consequently, considering the spatio-temporal progression of dopamine depletion in PD patients, and the effects of dopaminergic therapies on different frontostriatal circuits in diverse stages of PD, further studies with different tasks (evaluating both cognitive and affective components of ToM ability) and with patients at diverse stages of PD are needed to establish the influence of dopaminergic therapy on ToM functioning in the disease.

6. Conclusions

Although the findings in this field are not exhaustive, they provide some preliminary evidence that ToM difficulties may occur in PD patients. They also offer evidence that these difficulties principally involve the cognitive component of ToM, while the spatio–temporal progression of dopamine depletion allows us to hypothesize that the affective component may only be affected in advanced stages of the disease. Ad hoc studies comparing performance by early and advanced PD patients in tasks of affective and cognitive ToM are needed to better explain factors influencing ToM functioning in PD patients. In particular, the influence of neuropsychological functioning and psychiatric symptoms needs to be explored. As previously stated by Bloom and German [19] and by Adenzato et al. [2], in all probability, false belief tests are not appropriate to study the key issue of the relationship between ToM and executive functions. Future research should make use of the tasks able to disentangle the specific contribution of ToM processing from the contribution of other processing resources (e.g. attention and working memory). Furthermore, we suggest that for a deeper comprehension of the ToM profile in PD patients’ future research should correlate ToM performances with clinical measures of disease severity, disease duration, as well as levodopa equivalent daily dose. Neurorimag could also prove helpful to understand the mechanisms of ToM dysfunction in PD patients, and clarify whether different impairments of frontostriatal circuits are related to different impairments in ToM processes. Accordingly, future research should incorporate both structural and functional neurorimag data in the experimental setting.

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