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Impairments in Social Cognition in Early Medicated and Unmedicated Parkinson Disease

Maria Roca, PsyD,* † Teresa Torralva, PsyD,* † Ezequiel Gleichgerrcht, BSc,*
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(Cog Behav Neurol 2010;00:000-000)

Early recognition and effective management of the nonmotor symptoms of Parkinson disease (PD) is integral to the quality of life of both patients and caregivers. Earlier research has shown social interaction problems in patients with PD, and even though cognitive impairment in the early stages of the disease may be subtle and difficult to detect with classic neuropsychologic tests, the presence of early cognitive changes in PD is now well established, with executive function deficits being the most frequently reported cognitive symptom in this population.2-3

Theory of mind (ToM) is commonly defined as the ability to infer others’ mental states, including intentions and feelings, and it underlies important abilities such as the capacity to properly engage in social interaction.5 This crucial social ability has been extensively studied in patients with autistic disorder and other neuropsychiatric and neurologic conditions.6-13

Different subcomponents of ToM have also been defined, and some authors further split ToM into its cognitive and affective components.6,14-18 Although cognitive ToM refers to the capacity to infer others’ beliefs and intentions (cold aspects of ToM), affective ToM implies the ability to appreciate others’ emotional states (hot aspects of ToM). To “have ToM,” one must be able to attribute the intentions and affective mental states of others, and understand that those intentions and affective mental states may differ from one’s own.

Different tasks have been proposed to measure such unique human capacities, allowing for the differential assessment of the cognitive and the affective aspects of ToM. One such widely used task is the “Reading Mind in the Eyes,” introduced by Baron-Cohen et al in 1997, which was originally developed to measure ToM in patients with high-functioning Asperger syndrome. This task requires the subject to infer subtle affective and epistemic mental states based on pictures of the region around the eyes. Another example of how to test for ToM deficits in adults is the Faux Pas task, which evaluates whether subjects can recognize when someone unintentionally says something that would be hurtful or insulting.6 The Faux Pas was designed to differentially assess both cognitive and affective aspects of ToM.
Several brain structures including but not limited to the superior temporal sulcus, the temporal poles, the amygdala, and the prefrontal cortex (PFC) have been linked to this capacity of inferring the mental states of others.\textsuperscript{6,19–25} Within the PFC itself, although the ventromedial PFC has been linked to affective ToM, the dorsolateral PFC has been associated with the cognitive subcomponent of this function.\textsuperscript{16,17,26–28}

Even if the studies of ToM in PD are to date, limited, they all suggest deficits in this function, at least in the more advanced stages of the disease.\textsuperscript{29–32} However, most of these studies did not feature populations of patients with early PD and disregarded the studying of some important clinical variables, such as disease duration or the intake of dopaminergic medication. What is more, the majority of the studies of ToM in PD did not analyze the affective and cognitive subcomponents of this function separately, thus overlooking potentially different ToM profiles within this patient population.

Pe`ron et al\textsuperscript{32} investigated the different subcomponents of ToM in early and advanced PD, showing that in the more advanced patients, deficits were related particularly with the cognitive aspect of this function and affective ToM was not impaired. Although this study was the first to report differences in cognitive and affective ToM in PD patients, it failed to find deficits in patients with early PD, which suggested that ToM is spared during the early stages of the disease. However, the small sample size of early PD patients and the use of abbreviated forms of ToM tests may have decreased the sensitivity of the tasks to detect ToM deficits in the PD population.

As mentioned above, executive dysfunction is the most common cognitive symptom in early PD and contradictory results have been found regarding its association with ToM deficits in this population. Although some of the studies reported significant correlations between ToM and executive functions,\textsuperscript{29,30,32} others did not find said correlations.\textsuperscript{31}

The main aim of this study was to further investigate ToM and its different subcomponents in patients with early PD. In addition, we examined the relationship between ToM and executive functioning and other important clinical variables such as disease duration and intake of dopaminergic medication. For the purposes of this study, 36 patients with early PD were assessed with 2 widely used ToM tasks designed to detect subtle ToM deficits, and with a neuropsychologic battery which included classic executive tests. With the objective of further understanding ToM disturbances in this population, the performance of medicated and unmedicated PD patients was also compared.

\section*{METHODS}

\section*{Participants

\subsection*{Patients

Thirty-six patients who met UK Parkinson Disease Society Brain Bank criteria, between Hoehn and Yahr stages I and II were recruited from the Institute of Cognitive Neurology Data Base in Buenos Aires, Argentina and from the Movement Disorders Clinic at the Institute of Neuroscience of the Favaloro Foundation. Mean (± SD) age for the patient population was 63.4 years (± 10.3 y). Information on disease history and drug therapy was obtained by neurologists specialized in studying PD (A.C., G.G.A., and O.G.). Patients with different neurologic diagnoses or presenting radiologic structural brain abnormalities compatible with diagnoses other than PD were excluded from this study. Patients who scored less than 24 on the Mini-Mental State Examination\textsuperscript{33} were also excluded from the study to ensure the overall cognitive functioning of patients. Of these patients, 16 were under pharmacologic treatment either with levodopa or a dopamine agonist, and were thus included in the medicated group for further analysis. Assessment was conducted during the “on” state of the medication. Twenty of the patients were not taking any medication for their motor symptoms and were therefore included in the unmedicated group. Clinical and demographic data is included in Table 1.

Healthy control volunteers (n = 35) were obtained through word of mouth and were matched with patients for age and level of education. Participants were included in the control group if they reported no history of neurologic or psychiatric disorders, including traumatic brain injury or substance abuse. Demographic data of control subjects are included in Table 1.

\begin{table}[h]
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\caption{Clinical and Demographical Data of PD Patients and Control Subjects}
\begin{tabular}{l|ll|ll|ll}
\hline
 & \multicolumn{2}{c}{Medicated (n = 16)} & \multicolumn{2}{c}{Unmedicated (n = 20)} & \multicolumn{2}{c}{Control Subjects (n = 35)} \\
\hline
 & Mean & SD & Mean & SD & Mean & SD \\
\hline
Age (y) & 63.4 & 8.47 & 63.5 & 11.8 & 60.4 & 11.6 \\
Education (y) & 14.2 & 4.1 & 12.3 & 4.9 & — & — \\
Hoehn and Yahr & 1.42 & 0.57 & 1.33 & 0.54 & — & — \\
Disease duration (y) & 1.69 & 1.55 & 1.23 & 1.56 & — & — \\
Levodopa equivalents daily dose (mg) & 317.01 & 256.04 & — & — & — & — \\
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PD indicates Parkinson disease.
Procedure

Permission for the study was initially obtained from the local research ethics committee and all participants signed an informed consent before their inclusion in this study.

Neuropsychologic Testing

All PD patients were assessed using a complete neuropsychologic battery that featured tests of language including Categorical and Phonologic verbal fluency, a short version of the Boston Naming Test, and a short version of the Token Test. Memory was assessed with the Rey auditory verbal learning test and the delayed recall of the complex Rey Figure. Praxis was assessed with the copy of the Complex Rey Figure and attention; and executive functions were assessed with the Trail Making Test (TMT) A and B. Digit forward and backwards span, and the Wisconsin Card Sorting Test. To control for mood symptoms, the Beck Depression Inventory (BDI) was administered to all patients.

ToM Assessment

Reading the Mind in the Eyes Test

In this study, we used 15 affective stimuli of the original task in which participants must make inferences about affective mental states. The task consisted of photographs of the region around the eyes of a person, and participants were required to choose between 2 adjectives for the one that best described what the individual in the picture was thinking or feeling. The proposed adjectives were always antonyms (eg, “concerned/unconcerned”). Total score for this task was calculated as the number of items correctly identified. Data for this test was available for 34 patients.

Faux Pas Test

In this test, participants read a story that may or may not contain a social faux pas. The stories were placed in front of the participants so that they could refer back to it as needed, therefore reducing the demands on working memory. Ten stories contained a faux pas and the other 10 stories did not contain a faux pas. In the stimuli stories containing a faux pas, the character committing the faux pas was unaware that he or she had said something inappropriate, whereas the person in the story hearing it might have felt hurt or insulted. After each story was read, participants were asked whether something inappropriate had been said, and if so, why it was inappropriate. Performance was scored regarding the adequate identification of the faux pas (hits) and the adequate rejection of those stories which did not contain a faux pas (rejects). The score was 1 point for each faux pas correctly identified (maximum: 10), or non-faux pas correctly rejected (maximum: 10). When a faux pas was correctly identified, subjects were also asked 2 additional questions to measure intentionality—that is, recognizing that the person committing the faux pas was unaware that they had said something inappropriate (maximum 10)—and emotional attribution, in which participants should recognize that the person hearing the faux pas might have felt hurt or insulted (maximum 10). Data on this test was available for 35 of the patients.

Statistical Analysis

Comparisons across the 3 groups were conducted using 1-way analyses of variance with Bonferroni post-hoc comparisons when relevant. When 2 groups were compared at a time Student t test was used. When equal variances could not be assumed, nonparametric analysis was conducted, with Kruskal Wallis H test for comparison of more than 2 groups, and Mann-Whitney U test for group-to-group contrasts. For categorical variables (eg, sex), the Fisher exact probability test was used. Spearman coefficient was used for correlation between variables. All statistical analyses were performed using the SPSS 15.0.

RESULTS

Demographics

No significant differences were found across the groups for age (F2,71 = 1.96, P = 0.15), years of education (F2,71 = 1.7, P = 0.27), or sex (χ2 = 4.52, df = 2, P = 0.12). Medicated and unmedicated PD patients did not differ in terms of their Hoehn and Yahr stage (U = 72.5, P = 0.72) or in terms of their disease duration (t29 = 0.28, P = 0.78). No significant differences were found on the BDI (F2,71 = 1.32, P = 0.58) between medicated patients (mean = 9.13, SD = 6.1), unmedicated patients (mean = 9.23, SD = 5.0), and controls (mean = 5.13, SD = 1.2).

Neuropsychologic Profile

Patients’ neuropsychologic performance was examined looking at z scores, calculated based on age and sex-matched normative data. As expected, PD patients showed the greater impairments on tasks of executive functions, particularly on those of mental flexibility (Wisconsin Card Sorting Test: Mean z = −1.79) but within-normal performance on other executive tasks (TMT-B: mean z = −1.27; phonologic fluency: mean z = −1.15; and digit span backward: mean z = 0.66). Visuospatial abilities were also relatively affected (Figure Rey copy: mean z = −1.55) whereas patients showed relatively spared memory performance for both verbal (Rey auditory verbal learning test delayed: mean z = −0.86; recognition: mean z = −1.24) and nonverbal (Rey Figure delayed: mean z = −0.53) stimuli. Normal language scores were also revealed by performance on tasks of verbal comprehension (Token: mean z = −0.65), picture naming (Boston Naming Test: mean z = −0.95), and semantic fluency (mean z = −0.91). On tasks of attention, they also performed within the normal range (digit span forward: mean z = −1.15 and TMT-A: mean z = −1.14). When neuropsychologic performance of medicated and unmedicated patients was compared, no significant differences were found as shown in Table 2.
ToM Tasks

Mind in the Eyes

When comparing total performance between PD patients and controls, no significant differences were found on the Mind in the Eyes task \( \chi^2 = 2.85, df = 1, P = 0.12 \). There were no significant correlations between performance on ToM tasks and clinical measures such as disease severity, disease duration, or levodopa equivalent daily dose. When the whole patient group was analyzed, no correlations were found between performance on this task and executive functions tasks or BDI scores, as it is shown in Table 3.

When performance was compared between medicated and unmedicated PD patients, as well as control subjects, no significant differences were found across the groups on the hits \( \chi^2 = 2.20, df = 2, P = 0.33 \) or rejects \( \chi^2 = 2.81, df = 2, P = 0.25 \) scores on the Faux Pas. However, when analyzing the total score on this task, a significant difference was found across the groups \( \chi^2 = 6.98, df = 2, P = 0.03 \), with controls significantly outperforming medicated \( U = 89.0, P < 0.01 \) but not unmedicated \( U = 153.5, P = 0.14 \) PD patients. When analyzing the affective and cognitive subcomponents of the Faux Pas separately, again, no significant differences were found.

Faux Pas

When comparing performance between PD patients and control subjects, a significant effect was found on the Faux Pas Total Score \( U = 242.5, P = 0.017 \). Significant differences also emerged on the hits \( U = 437.00, P = 0.04 \) and on the intentionality scores \( U = 183.0, P < 0.01 \), whereas no significant differences were observed neither on the reject score \( U = 490.0, P = 0.13 \) nor on the emotional attribution score \( U = 386.5, P = 0.13 \). Again, no correlations were found between the total score of this task and performance on executive functions tasks or BDI scores (Table 3).

As shown in Table 4, when performance was analyzed between medicated and unmedicated PD patients, as well as control subjects, no significant differences were found across the groups on the hits \( \chi^2 = 2.20, df = 2, P = 0.33 \) or rejects \( \chi^2 = 2.81, df = 2, P = 0.25 \) scores on the Faux Pas. However, when analyzing the total score on this task, a significant difference was found across the groups \( \chi^2 = 6.98, df = 2, P = 0.03 \), with controls significantly outperforming medicated \( U = 89.0, P < 0.01 \) but not unmedicated \( U = 153.5, P = 0.14 \) PD patients. When analyzing the affective and cognitive subcomponents of the Faux Pas separately, again, no significant differences were found.
TABLE 4. Mean (SD) Scores For the Theory of Mind Tasks Included in the Study

<table>
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<tr>
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<th>Unmedicated PD</th>
<th>Healthy Controls</th>
<th>Group Comparisons</th>
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<tr>
<td>Faux pas (total score Max = 20)</td>
<td>17.3 (2.0)</td>
<td>17.9 (2.0)</td>
<td>18.9 (1.0)</td>
<td>$\chi^2 = 6.98$, $P &lt; 0.05$††</td>
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<td>Hit score (Max = 10)</td>
<td>8.27 (2.0)</td>
<td>8.26 (2.1)</td>
<td>9.25 (1.0)</td>
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<td>Reject score (Max = 10)</td>
<td>9.00 (1.3)</td>
<td>9.63 (0.5)</td>
<td>9.78 (0.5)</td>
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<td>Intentionality score (Max = 10)</td>
<td>6.40 (2.6)</td>
<td>6.17 (1.4)</td>
<td>8.56 (1.6)</td>
<td>$U = 49.0$, $P &lt; 0.01$†</td>
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<tr>
<td>Emotion attribution score (Max = 10)</td>
<td>7.07 (2.6)</td>
<td>6.78 (2.4)</td>
<td>7.48 (2.5)</td>
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<td>Mind in the eyes (total score Max = 15)</td>
<td>12.3 (1.5)</td>
<td>12.4 (1.6)</td>
<td>13.0 (1.0)</td>
<td>$\chi^2 = 2.45$, $P = 0.29$</td>
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*Medicated PD versus controls, $P < 0.01$
†Unmedicated PD versus controls, $P < 0.01$.

PD indicates Parkinson disease.

This study revealed that deficits on ToM can be found in early PD patients. In line with earlier findings in patients with more advanced PD, these deficits were found specifically on the cognitive aspects of this function, whereas no significant differences were found for the affective measures of ToM. Although early PD patients were not impaired on their capacity to understand that someone must feel hurt or insulted after a social faux pas, they failed on their ability to attribute intentionality to the person committing it. Importantly, there seems to be no relationship between said deficits and performance on executive functioning, level of depressive symptoms, or medication intake.

Saltzman et al. were the first group to report ToM deficits in patients with PD and to investigate their relationship to executive dysfunction, by comparing the performance of 11 nondemented PD patients against the performance of 2 healthy control groups: an elderly group and a group of university-aged participants. Although this was a pioneer study, a major limitation to the generalization of its results lies on the fact that the group of PD patients included only medicated patients in the stages associated with ratings of II or III points on the Hoehn and Yahr scale. A second study by Mengelberg and Siegert also investigated ToM in PD and again included patients in stages II, III, and IV, and pooled medicated and not medicated patients into the same group. Moreover, none of these studies assessed the cognitive and affective aspects of ToM separately.

As already mentioned, Péron et al’s study used an abbreviated version of the faux pas which could potentially decrease its sensitivity and assessed the same early PD patients in both the on and “off” condition possibly inducing a learning effect. Our study shows that when more comprehensive — and thus, more sensitive — tests are used, deficits on cognitive ToM can also be detected in the early stages of the disease. This finding is particularly important, because although earlier studies had already reported the presence of ToM deficits in patients with more advanced stages of the disease, to our knowledge, this is the first study to replicate such findings in patients in the early stages.

Our results suggest that early on the disease, only cognitive ToM is affected in PD. However, these deficits seem to be subtle and can only be detected when extensive and comprehensive tests of ToM are administered. If we integrate our results with those of Péron et al’s, it can be suggested that as the disease progresses, those deficits in cognitive ToM become more prominent and thus detectable by less sensitive tasks. Moreover, Bodden et al. suggested that, as PD advances, the affective aspects of this function also become compromised. These findings may be explained by taking in consideration the differential deterioration of the fronto-striatal circuits during the course of PD. Although the original deficits on cognitive ToM can be related to the deterioration of the dorsolateral prefrontal-striatal circuitry, which occurs early in the disease, the later deterioration of the fronto-striatal-limbic circuitry, closely related to the ventromedial PFC, may account for the deficits found in affective ToM in patients during the more advanced stages of the disease (For a review see Bodden et al.). This hypothesis goes in line with earlier neuroimaging and...
lesion studies data which have linked the dorsolateral PFC with cognitive ToM and the ventromedial PFC with the affective aspect of this function.\(^\text{16,17,26–28}\) Future studies will have to contribute to the understanding of the dorsolateral versus ventromedial circuitry in the components of ToM in PD patients.

Despite the fact that PD primarily affects the motor system, it is now well established that even in early PD,\(^\text{43,44}\) cognitive dysfunction is present. Although a range of other memory and learning impairments are also evident (eg. Muslimovic, 2005), the executive deficits found in early PD are similar to those observed after PFC dysfunction, which include impairments in working memory,\(^\text{3}\) planning and set-shifting,\(^\text{3,45}\) and other executive deficits.\(^\text{2–5}\) The similarity of such deficits in PD and the ones found after PFC dysfunction has been mainly explained also by the disruption of the reciprocal loops between the striatum and the PFC.\(^\text{44–46}\)

Different executive tests were used in this study to investigate the relationship between participants’ performance on ToM test and executive dysfunction. The profile of the executive deficits found in our early PD patients was largely consistent with earlier studies. However, none of these deficits correlated with any of the ToM measures, strongly indicating that abnormal cognitive ToM is not related to the executive dysfunction exhibited by the patients. In agreement with our recent findings in patients with prefrontal dysfunction,\(^\text{13}\) a number of earlier studies have also demonstrated dissociations in performance on ToM and traditional executive tasks\(^\text{8,47,48}\) suggesting that executive functions and social cognition, although sharing some neural basis, are 2 separate cognitive domains.

It has been also suggested that dopaminergic and serotoninergic dysfunctions are responsible for ToM deficits.\(^\text{20}\) Even if it is acknowledged that the dopaminergic system is involved in areas critical for intact ToM, and that deficits on this domain have been described in populations with dopamine affection, the exact relationship between dopamine and ToM has not yet been fully established. It must be emphasized that our study was not designed to determine the role of dopamine in ToM, and therefore, further studies will be needed to clarify this issue. We did not find significant differences between medicated and unmedicated patients with PD, and no significant correlations were found between ToM performance and the levodopa equivalent daily dose within the medicated group.

There are limitations of our study that need to be acknowledged. Although a within-patient design using an on/off dopamine manipulation would have provided stronger evidence concerning the role of dopamine in social cognition, the main purpose of this study was to detect deficits in ToM in early PD and not to disentangle the role of dopamine in this important cognitive function. Another shortcoming of this study is the lack of measures that can detect the real impact that ToM deficits have on patients’ everyday life. For this reason, it is suggested that future studies assess ToM by also investigating the relatives’ and caregivers’ perception of changes regarding this function in patients.

In summary, the body of knowledge regarding ToM in people with PD is not large, the few studies that have been carried out in this field had previously shown that PD patients have deficits in ToM in the more advanced stages of the disease, and specifically in the cognitive aspect of this domain. This is the first study to reveal that cognitive ToM deficits can also be found in the early stages of the disease. Yet, further research is needed to determine the exact nature and the real impact of these deficits, and to determine its relation with the fronto-striatal system.

Finally, it must be noted that the impairments on social cognition in this study were not captured with standard cognitive tests, but rather with a specific social cognition battery. From a clinical perspective, our results have clear implications for the clinical assessment of PD patients, because, as traditional cognitive tests do not capture a full range of abnormalities in social cognition. We suggest that a comprehensive cognitive assessment in early PD should include social cognition tests. The recognition of ToM impairments in early PD is important, as these deficits may impact patients’ social interactions and quality of life.

ACKNOWLEDGMENT

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