Theory of Mind in Parkinson's disease

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Short Title:

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Abstract

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 are discussed, as well as the relationships between frontostriatal circuits and ToM processing.

Keywords: Basal ganglia, Executive functions, Frontostriatal circuits, Parkinson's disease, Social cognition, Theory of Mind.

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, and visuospatial functions [1, 74]. In the present study, we review the literature on a new field of interest, which has emerged in the study of the cognitive profile of patients with PD: Theory of Mind (ToM) ability, i.e., the ability to understand and predict other people's behavior by attributing independent mental states to them [13, 66, 85].

Usually studied in subjects with various psychiatric disorders such as schizophrenia [23, 102], autism [15, 24], depression [57, 103], and borderline personality disorder [10, 45], in recent years researchers have also started assessing ToM ability in patients with neurodegenerative diseases [2, 20, 63]. In particular, ToM was recently assessed in PD patients to evaluate how PD-related neuropathology and dopaminergic replacement therapy may affect the subcortical (amygdala and basal ganglia) and cortical structures (principally the medial prefrontal cortex) involved in the processing of socially relevant information.

The present paper provides a review of the current evidence on ToM ability in patients with PD without dementia. The ten studies included were identified through searches in the ISI Web of knowledge, Medline, and PsycINFO electronic databases, and only the studies available in English were included. The final search for this review was carried out in September 2010. The keywords used for the search were Parkinson's disease combined with each of the following terms: mentalizing, mindreading, and theory of mind. Only the studies

where the performance of non-demented PD patients was compared to that of healthy controls or other clinical populations were included. In addition, patients also had to be diagnosed according to the accepted consensus guidelines for clinical or pathological diagnosis and had to be minimally matched on the variables of age and cognitive functioning.

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 Figure 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; the *anterior cingulate circuit*, including the anterior cingulate cortex (ACC), the striatum (ventromedial caudate nucleus, ventral putamen), the nucleus accumbens, the olfactory tubercle, the globus pallidus (rostromedial), and the thalamus [17].

Figure 1 about here

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 reversal learning, associated with the orbital frontostriatal circuit [36]. Because the effect of l-dopa depends mainly on its ability to elevate dopamine levels in the striatum [68], the observed effects on task-set switching and reversal learning are

most likely due to effects of dopamine in the dorsal and ventral striatum, respectively, which are connected to different cortical areas via segregated frontostriatal circuits [6]. This double dissociation is evident when directly comparing patients 'on' and 'off' medication and is in line with the 'dopamine overdose hypothesis' [53–54, 98], according to which administration of dopaminergic medication to PD patients may replenish dopamine depleted circuits but overdose relatively intact circuits. Consequently, in the early stages of PD, treatment with l-dopa has a beneficial effect on the cognitive processes based on the dorsolateral frontostriatal circuit [79]; however, it has a detrimental effect on the processes based on the orbital frontostriatal circuit, such as decision making [83].

3. Prefrontal cortex and Theory of Mind tasks

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 (ToM), 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 circuit affected in PD, was listed as one of the areas involved in ToM processing [7].

The use of different ToM tasks has shown that the inference on other people's feelings (affective component) and beliefs (cognitive component) engage the PFC differently [92]. Accordingly, recent studies suggest an advanced view for the complex concept we refer to as ToM: the different engagement of the PFC may reflect different ToM processes depending on the nature of the mental state that is inferred. It may therefore be appropriate to talk about an affective ToM subcomponent (belief about feelings) and a cognitive ToM subcomponent (belief about belief) [59, 94]. It has been suggested that cognitive and affective ToM depend on distinct neural structures that can be selectively disrupted: whereas the ventromedial prefrontal cortex has an important role in processing affective ToM [92], the DLPFC 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).

Insert table 1 about here

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 and colleagues [81] after deep brain stimulation (DBS), only the study by Bodden and colleagues [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 Euteneuer 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 and colleagues, 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 and colleagues [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 and colleagues [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 and colleagues [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 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 about 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 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 and colleagues [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 and colleagues 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 and colleagues [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 and colleagues [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 and colleagues [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 those frontostriatal 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 and colleagues [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. Neuroimaging 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 neuroimaging data in the experimental setting.

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References

[1] Aarsland D, Bronnick K, Larsen JP, Tysnes OB, Alves G. Cognitive impairment in incident, untreated Parkinson's disease: the Norwegian ParkWest Study. Neurology 2009; 72: 1121-6.

[2] Adenzato M, Cavallo M, Enrici I. Theory of Mind ability in the behavioural variant of frontotemporal dementia: an analysis of the neural, cognitive, and social levels. Neuropsychologia 2010; 48: 2-12.

[3] Adolphs R. The neurobiology of social cognition. Curr Opin Neurobiol 2001; 11: 231-9.

[4] Adolphs R. The social brain: neural basis of social knowledge. Annu Rev Psychol 2009; 60: 693-716.

[5] Albin RL, Young AB, Penney JB. The functional-anatomy of basal ganglia disorders. Trends Neurosci 1989; 12: 366-75.

[6] Alexander GE, Delong MR, Strick PL. Parallel organisation of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 1986; 9: 357-81.

[7] Amodio DM, Frith CD. Meeting of minds: the medial frontal cortex and social cognition. Nat Rev Neurosci 2006; 7: 268-77.

[8] Apperly IA, Samson D, Humphreys GW. Domain-specificity and theory of mind: evaluating neuropsychological evidence. Trends Cogn Sci 2005; 9: 572-7.

[9] Ardila A. On the evolutionary origins of executive functions. Brain Cogn 2008; 68: 92-9.

[10] Arntz A, Bernstein D, Oorschot M, Schobre P. Theory of Mind in borderline and cluster-C personality disorder. J Nerv Ment Dis 2009; 197: 801-7.

[11] Bara BG, Ciaramidaro A, Walter H, Adenzato M. Intentional minds: a philosophical analysis of intention tested through fMRI experiments involving people with

schizophrenia, people with autism, and healthy individuals. Front Human Neurosci In press.

[12] Baron-Cohen S. The autistic child's Theory of Mind: a case of specific developmental delay. J Child Psychol Psychiatry 1989; 30: 285-98.

[13] Baron-Cohen S. Mindblindness: an essay on autism and Theory of Mind. Cambridge: MIT Press; 1995.

[14] Baron-Cohen S, Jolliffe T, Mortimore C, Robertson M. Another advanced test of Theory of Mind: evidence from very high functioning adults with autism or Asperger syndrome. J Child Psychol Psychiatry 1997; 38: 813-22.

[15] Baron-Cohen S, Leslie AM, Frith U. Does the autistic child have a 'theory of mind'? Cognition 1985; 21: 37-46.

[16] Baron-Cohen S, Wheelwright S, Hill J, Raste Y, Plumb I. The "Reading the Mind in the Eyes" Test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. J Child Psychol Psychiatry 2001; 42: 241-51.

[17] Bernheimer H, Birkmayer W, Hornykiewicz O, Jellinger K, Seitelberger F. Brain dopamine and the syndromes of Parkinson and Huntington: clinical, morphological and neurochemical correlations. J Neurol Sci 1973; 20: 415-55.

[18] Bird CM, Castelli F, Malik O, Frith U, Husain M. The impact of extensive medial frontal lobe damage on 'Theory of Mind' and cognition. Brain 2004; 127: 914-28.

[19] Bloom P, German TP. Two reasons to abandon the false belief task as a test of Theory of Mind. Cognition 2000; 77: B25-B31.

[20] Bodden ME, Dodel R, Kalbe E. Theory of Mind in Parkinson's disease and related basal ganglia disorders: a systematic review. Mov Disord 2010; 25: 13-27.

[21] Bodden ME, Mollenhauer B, Trenkwalder C, Cabanel C, Eggert KM, Unger MM, et al. Affective and cognitive Theory of Mind in patients with Parkinson's disease. Parkinsonism Relat Disord 2010; 16: 466-70.

[22] Bonelli R, Cummings JL. Frontal-subcortical circuitry and behavior. Dialogues Clin Neurosci 2007; 9: 141-51.

[23] Brune M. Theory of Mind in schizophrenia: a review of the literature. Schizophr Bull 2005; 31: 21–42.

[24] Brune M, Brune-Cohrs U. Theory of Mind: evolution, ontogeny, brain mechanisms and psychopathology. Neurosci Biobehav Rev 2006; 30: 437-55.

[25] Brunet E, Sarfati Y, Hardy-Bayle MC, Decety J. A PET investigation of the attribution of intentions with a nonverbal task. NeuroImage 2000; 11: 157-66.

[26] Bublak P, Muller U, Gron G, Reuter M, von Cramon DY. Manipulation of working memory information is impaired in Parkinson's disease and related to working memory capacity. Neuropsychology 2002; 16: 577-90.

[27] Carlson SM, Moses LJ, Breton C. How specific is the relation between executive function and Theory of Mind? Contributions of inhibitory control and working memory. Infant Child Dev 2002; 11: 73-92.

[28] Champagne-Lavau M, Joanette Y. Pragmatics, Theory of Mind and executive functions after a right hemisphere lesion: different patterns of deficits. J Neurolinguistics 2009; 22: 413-26.

[29] Chandler M, Lalonde C. Shifting to an interpretative Theory of Mind: 5-to-7 year olds' changing conceptions of mental life. In: Sameroff AJ, Faith MM, editors. The five to seven year shift. The age of reason and responsibility, Chicago: University of Chicago Press; 1996, p. 111-39.

[30] Chaudhury KR, Healy DG, Schapira AHV. Non motor symptoms of Parkinson's disease: diagnosis and management. Lancet Neurol 2006; 5: 235-45.

[31] Chudasama Y, Robbins TW. Functions of frontostriatal systems in cognition: comparative neuropsychopharmacological studies in rats, monkeys and humans. Biol Psychol 2006; 73: 19-38.

[32] Ciaramidaro A, Adenzato M, Enrici I, Erk S, Pia L, Bara BG, et al. The intentional network: how the brain reads varieties of intentions. Neuropsychologia 2007; 45: 3105-13.

[33] Cools R. Dopaminergic modulation of cognitive function-implications for L-DOPA treatment in Parkinson's disease. Neurosci Biobehav Rev 2006; 30: 1-23.

[34] Cools R, Altamirano L, D'Esposito M. Reversal learning in Parkinson's disease depends on medication status and outcome valence. Neuropsychologia 2006; 44: 1663-73.

[35] Cools R, Barker RA, Sahakian BJ, Robbins TW. Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. Cereb Cortex 2001; 11: 1136-43.

[36] Cools R, Barker RA, Sahakian BJ, Robbins TW. L-Dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease. Neuropsychologia 2003; 41: 1431-41.

[37] Cools R, Barker RA, Sahakian BJ, Robbins TW. Mechanisms of cognitive set flexibility in Parkinson's disease. Brain 2001; 124: 2503-12.

[38] Cools R, Lewis SJ, Clark L, Barker RA, Robbins TW. L-DOPA disrupts activity in the nucleus accumbens during reversal learning in Parkinson's disease. Neuropsychopharmacology 2007; 32: 180-9.

[39] Cooper CA, Mikos AE, Wood MF, Kirsch-Darrow L, Jacobson CE, Okun MS, et al. Does laterality of motor impairment tell us something about cognition in Parkinson's disease? Parkinsonism Relat Disord 2009; 15: 315-7.

[40] Delong MR. Primate models of movement-disorders of basal ganglia origin. Trends Neurosci 1990; 13: 281-85.

[41] Dennis M, Agostino A, Roncadin C, Levin H. Theory of Mind depends on domain general executive functions of working memory and cognitive inhibition in children with traumatic brain injury. J Clin Exp Neuropsychol 2009; 31: 835-47.

[42] Ellfolk U, Karrasch M, Laine M, Pesonen M, Krause CM. Event-related desynchronization/synchronization during an auditory verbal working memory task in mild Parkinson's disease. Clin Neurophysiol 2006; 117: 1737-45.

[43] Enrici I, Adenzato M, Cappa S, Bara BG, Tettamanti M. Intention processing in communication: a common brain network for language and gestures. J Cogn Neurosci In press; doi:10.1162/jocn.2010.21594.

[44] Euteneur F, Schaefer F, Stuermer R, Boucsein W, Timmermann L, Barbe MT, et al. Dissociation of decision making under ambiguity and decision making under risk in patients with Parkinson's disease: a neuropsychological and psychophysiological study. Neuropsychologia 2009; 47: 2882-90.

[45] Fertuck EA, Jekal A, Song I, Wyman B, Morris MC, Wilson ST. Enhanced 'Reading the Mind in the Eyes' in borderline personality disorder compared to healthy controls. Psychol Med 2009; 39: 1979-88.

[46] Fine C, Lumsden J, Blair RJR. Dissociation between 'Theory of Mind' and executive functions in a patient with early left amygdala damage. Brain 2001; 124: 287-98.

[47] Frank MJ, Seeberger LC, O'Reilly RC. By carrot or by stick: cognitive reinforcement learning in parkinsonism. Science 2004; 306: 1940-43.

[48] Gallagher HL, Jack AI, Roepstroff A, Frith CD. Imaging the intentional stance in a competitive game. NeuroImage 2002; 16: 814-21.

[49] Gallese V, Goldman A. Mirror neurons and the simulation theory of mind-reading. Trends Cogn Sci 1999; 2: 493–501.

[50] Gaspar P, Berger B, Febvret A, Vigny A, Henry JP. Catecholamine innervation of the human cerebral-cortex as revealed by comparative immunohistochemistry of tyrosine-hydroxylase and dopamine-beta-hydroxylase. J Comp Neurol 1989; 279: 249-71.

[51] Gilbert B, Belleville S, Bherer L, Chouinard S. Study of verbal working memory in patients with Parkinson's disease. Neuropsychology 2005; 19: 106-14.

[52] Gopnik A, Wellmann H. Why the child's theory really is a theory. Mind Lang 1992; 7: 145–51.

[53] Gotham AM, Brown RG, Marsden CD. Levodopa treatment may benefit or impair frontal function in Parkinson's disease. Lancet 1986; 2: 970-1.

[54] Gotham AM, Brown RG, Marsden CD. Frontal cognitive function in patients with Parkinson's disease "on" and "off" levodopa. Brain 1988; 111: 299-321.

[55] Hala S, Chandler M, Fritz AS. Fledgling theories of mind: deception as a marker of three years old understanding of false belief. Child Dev 1991; 62: 83-97.

[56] Hughes C, Ensor R. Executive function and Theory of Mind: predictive relations from ages 2 to 4. Dev Psychol 2007; 43: 1447-59.

[57] Inoue Y, Yamada K, Kanba S. Deficit in Theory of Mind is a risk for relapse of major depression. J Affect Disord 2006; 95: 125-7.

[58] Jankovic J. Parkinson's disease: clinical features and diagnosis. J Neurol Neurosurg Psychiatry 2008; 79:368-376.

[59] Kalbe E, Grabenhorst F, Brand M, Kessler J, Hilker R, Markowitsch HJ. Elevated emotional reactivity in affective but not cognitive components of theory of mind: a psychophysiological study. J Neuropsychol 2007; 1: 27–38.

[60] Kalbe E, Schlegel M, Sack AT, Nowak DA, Dafotakis M, Bangard C, Brand M, Shamay-Tsoory S, Onur OA, Kessler J. Dissociating cognitive from affective theory of mind: a TMS study. Cortex 2010; 46: 769-80.

[61] Katzen HL, Levin BE, Weiner W. Side and type of motor symptom influence cognition in Parkinson's disease. Mov Disord 2006; 21: 1947-53.

[62] Kawamura M, Koyama S. Social cognitive impairment in Parkinson's disease. J Neurol 2007; 254: 49-53.

[63] Kipps CM, Hodges JR. Theory of Mind in frontotemporal dementia. Soc Neurosci 2006; 1: 235-44.

[64] Kish SJ, Shannak K, Hornykiewicz O. Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinsons-disease. N Engl J Med 1988; 318: 876-880.

[65] Koerts J, Leenders KL, Brouwer WH. Cognitive dysfunction in non-demented Parkinson's disease patients: controlled and automatic behaviour. Cortex 2009; 45: 922-9.

[66] Leslie AM. Pretense and representation: the origins of 'Theory of Mind'. Psychol Rev 1987; 94: 412-26.

[67] Lieberman MD. Social cognitive neuroscience: a review of core processes. Annu Rev Psychol 2007; 58: 259–79.

[68] Maruyama W, Naoi M, Narabayashi H. The metabolism of L-Dopa and L-threo-3, 4-dihydroxyphreylserine and their effects on monoamines in the human brain: analysis of the intraventricular fluid from parkinsonian patients. J Neurol Sci 1996; 139: 141-8.

[69] Mengelberg A, Siegert RJ. Is Theory of Mind impaired in Parkinson's disease? Cogn Neuropsychiatry 2003; 8: 191-209.

[70] Middleton FA, Strick PL. Basal-ganglia projections to the prefrontal cortex of the primate. Cereb Cortex 2002; 12: 926-35.

[71] Mimura M, Oeda R, Kawamura M. Impaired decision-making in Parkinson's disease. Parkinsonism Relat Disord 2006; 12: 169-75.

[72] Monetta L, Grindrod CM, Pell MD. Irony comprehension and Theory of Mind deficits in patients with Parkinson's disease. Cortex 2009; 45: 972-81.

[73] Moses LJ, Carlson SM, Sabbagh MA. On the specificity of the relation between executive function and children's Theories of Mind. In: Schneider W, Schumann-Hengsteler R, Sodian B, editors. Young children's cognitive development: interrelationships among executive functioning, working memory, verbal ability and Theory of Mind, Mahwah, NJ: Erlbaum; 2005, p. 131-45.

[74] Muslimovic D, Post B, Speelman JD, Schmand B. Cognitive profile of patients with newly diagnosed Parkinson disease. Neurology 2005; 65: 1239-45.

[75] Olsson A, Ochsner KN. The role of social cognition in emotion. Trends Cogn Sci 2008; 12: 65-71.

[76] Owen AM. Cognitive dysfunction in Parkinson's disease: the role of frontostriatal circuitry. Neuroscientist 2004; 10: 525-37.

[77] Owen AM, Iddon JL, Hodges JR, Summers BA, Robbins TW. Spatial and non-spatial working memory at different stages of Parkinson's disease. Neuropsychologia 1997; 35: 519-32.

[78] Pardini M, Nichelli PF. Age-related decline in mentalizing skills across adult life span. Exp Aging Res 2009; 35: 98-106.

[79] Pascual-Sedano B, Kulisevsky J, Barbanoj M, Garcia-Sanchez C, Campolongo A, Gironell A, et al. Levodopa and executive performance in Parkinson's disease: a randomized study. J Int Neuropsychol Soc 2008; 14: 832-41.

[80] Perner J, Wimmer H. "John thinks that Mary thinks that…": attribution of second-order beliefs by 5- to 10-year-old children. J Exp Child Psychol 1985; 39 : 437-71.

[81] Peron J, Le Jeune F, Haegelen C, Dondaine, T., Drapier D, Sauleau P, et al. Subthalamic nucleus stimulation affects Theory of Mind network : a PET study in Parkinson's disease. PLoS One 2010; 5: e9919.

[82] Peron J, Vicente S, Leray E, Drapier S, Drapier D, Cohen R, et al. Are dopaminergic pathways involved in Theory of Mind? A study in Parkinson's disease. Neuropsychologia 2009; 47: 406-14.

[83] Poletti M, Frosini D, Lucetti C, Del Dotto P, Ceravolo P, Bonuccelli U. Decision making in de novo Parkinson's disease. Mov Disord 2010; 25: 1432-6.

[84] Povinelli DJ, Nelson KE, Boysen ST. Inferences about guessing and knowing by chimpanzees. J Comp Psychol 1990; 104: 203-10.

[85] Premack DG, Woodruff G. Does the chimpanzee have a Theory of Mind? Behav Brain Sci 1978; 1: 515-26.

[86] Roca M, Torralva T, Gleichgerrercht E, Chade A, Arevalo GG, Gershanik O, et al. Impairments in social cognition in early medicated and unmedicated Parkinson's disease. Cogn Behav Neurol 2010; 23: 152-8.

[87] Rowe AD, Bullock PR, Polkey CE, Morris RG. Theory of Mind impairments and their relationship to executive functioning following frontal lobe excisions. Brain 2001; 124: 600-16.

[88] Saltzman J, Strauss E, Hunter M, Archibald S. Theory of Mind and executive functions in normal human aging and Parkinson's disease. J Int Neuropsychol Soc 2000; 6: 781-8.

[89] Sawamoto N, Piccini P, Hotton G, Pavese N, Thielemans K, Brooks DJ. Cognitive deficits and striato-frontal dopamine release in Parkinson's disease. Brain 2008; 131: 1294-1302.

[90] Saxe R, Wexler A. Making sense of another mind: the role of the right temporoparietal junction. Neuropsychologia 2005; 43: 1391-9.

[91] Scatton B, Rouquier L, Javoy-Agid F, Agid Y. Dopamine deficiency in the cerebral-cortex in Parkinson disease. Neurology 1982; 32: 1039-1040.

[92] Shamay-Tsoory SG, Aharon-Peretz J. Dissociable prefrontal networks for cognitive and affective Theory of Mind: a lesion study. Neuropsychologia 2007; 45: 3054-67.

[93] Shamay-Tsoory SG, Tibi-Elhnanay Y, Aharon-Peretz J. The ventromedial prefrontal cortex is involved in understanding affective but not cognitive Theory of Mind stories. Soc Neurosci 2006; 1: 149-66.

[94] Shamay-Tsoory SG, Tomer R, Berger BD, Goldsher D, Aharon-Peretz J. Impaired affective Theory of Mind is associated with right ventromedial prefrontal damage. Cogn Behav Neurol 2005; 18: 55-67.

[95] Singer T. The neuronal basis and ontogeny of empathy and mind reading: review of literature and implications for future research. Neurosci Biobehav Rev 2006; 30: 855-63.

[96] Stone VE, Baron-Cohen S, Knight RT. Frontal lobe contributions to Theory of Mind. J Cogn Neurosci 1998; 10: 640-56.

[97] Stuss DT, Gallup GG Jr, Alexander MP. The frontal lobes are necessary for 'Theory of Mind'. Brain 2001; 124: 279-86.

[98] Swainson R, Rogers RD, Sahakian BJ, Summers BA, Polkey CE, Robbins TW. Probabilistic learning and reversal deficits in patients with Parkinson's disease or frontal or temporal lobe lesions: possible adverse effects of dopaminergic medication. Neuropsychologia 2000; 38: 596-612.

[99] Tomer R, Aharon-Peretz J, Tsitrinbaum Z. Dopamine asymmetry interacts with medication to affect cognition in Parkinson's disease. Neuropsychologia 2007; 45: 357-67.

[100] Van Overwalle F. Social cognition and the brain: a meta-analysis. Hum Brain Mapp 2009; 30: 829-58.

[101] Walter H, Adenzato M, Ciaramidaro A, Enrici I, Pia L, Bara BG. Understanding intentions in social interaction: the role of the anterior paracingulate cortex. J Cogn Neurosci 2004; 16: 1854-63.

[102] Walter H, Ciaramidaro A, Adenzato M, Vasic N, Ardito RB, Erk S, et al. Dysfunction of the social brain in schizophrenia is modulated by intention type: an fMRI study. Soc Cogn Affect Neurosci 2009; 4: 166-76.

[103] Wang YG, Wang YQ, Chen SL, Zhu CY, Wang K. Theory of Mind disability in major depression with or without psychotic symptoms: a componential view. Psychiatry Res 2008; 161: 153-61.

[104] Wimmer H, Perner J. Beliefs about beliefs: representation and constraining function of wrong beliefs in young children's understanding of deception. Cognition 1983; 13: 103-28.

[105] Zald DH, Andreotti C. Neuropsychological assessment of the orbital and ventromedial prefrontal cortex. Neuropsychologia 2010; 48: 3377-91.

Figures captions

Figure 1. Parallel organisation of functionally segregated circuits connecting the frontal cortex and striatum based on original scheme by Alexander et al. [6] and adapted by Chudasama and Robbins [31]. Four frontostriatal 'loops' are shown. Each 'loop' starts in a specific region of the frontal cortex and innervates different levels of the striatum before being relayed back to its cortical origin, via the thalamus. NB: short thin black arrows indicate dopaminergic (DA) innervation of the cortex and striatum. The diagram to the left of the dashed line indicates the general organisation of the cortico-striatal-pallidal-thalamic loop.

Abbreviations: GPi, internal segment of globus pallidus; SNr, substantia nigra pars reticulata; VP, ventral pallidum; MD, medialis dorsalis; MDpc, medialis dorsalis pars parvocellularis; MDmc, medialis dorsalis pars magnocellularis; VAmc, ventralis anterior pars magnocellularis; VApc, ventralis anterior pars parvocellularis; VLo, ventralis lateralis pars oralis; VLm, ventralis lateralis pars medialis; cl, caudolateral; ldm, lateral dorsalmedial; mdm, medial dorsomedial; pm, posteromedial; rd, rostrodorsal; rl, rostrolateral; rm, rostromedial.

Figure 1

Copyrighted image

See Figure 1 of Chudasama and Robbins [31]

Table 1

PD studies including Theory of Mind tasks. The order is chronological.

Authors	Sample	Patients' Mean age in years (SD)	Disease duration in years (SD)	LEDD/ DRT in mg (SD)	Hoen and Yahr stage	MMSE (SD)	Task	ToM component	Main results
Saltzman et al., 2000	11 PD 8 HC	71 (13.45)	N/A	N/A	2.5	Above 26	False beliefs	Cognitive	Impaired
							Spy task	Cognitive	Impaired
							Perspective taking	Cognitive	Preserved
							Deception task	Cognitive	Preserved
Mengelberg and Siegert, 2003	13 PD 11 HC	72.9 (8.9)	5.4	N/A	4 II 6 III 2 IV	28.46 (1.39)	False Beliefs	Cognitive	Impaired
							Short Passage task	Cognitive	Impaired
							First Order story	Cognitive	Impaired
							Second Order story	Cognitive	Preserved
Mimura et al., 2006	18 PD 40 HC	68.9 (7.0)	N/A	N/A	II/III	27.8 (1.9)	RME	Affective	Slightly impaired
Kawamura and Koyama, 2007	11 PD 20 HC	67.1	N/A	N/A	N/A	28.1 (2.6)	FPR	Cognitive and affective	Impaired cognitive component
Euteneuer et al., 2009	21 PD 23 HC	67.6 (7.3)	7.1 (6)	487 (317)	2.5	29 (1.10)	RME	Affective	Preserved
Monetta et al., 2009	11 PD 11 HC	67.1 (10.9)	9.1 (3.2)	N/A	2.5 (0.9)	140.3 (2.9) on MDRS	First Order story	Cognitive	Mostly preserved
							Second Order story	Cognitive	Impaired
Peron et al., 2009	17 early PD 26 HC	61.0 (7.1)	2.5 (1.5)	458 (337)	On 1.0 (0.9) Off 1.5 (0.7)	Early PD On 138.8 (4.4)	RME	Affective	Preserved
						Early PD Off 140 (4.5)	FPR	Cognitive and affective	Both preserved

	27 advanced PD 26 HC	56.6 (7.8)	10.2 (4.9)	1104 (509)	On 1.3 (0.9) Off 2.5 (1.0)	Advanced PD 139.1 (4.1) on MDRS	RME	Affective	Preserved
							FPR	Cognitive and affective	Impaired cognitive component
Bodden et al., 2010	21 PD 21 HC	63.7 (10.0)	5.1 (2.8)	432.1 (316.8)	2.5 (Range 1.0-3.0)	29 (Range 28-30)	RME	Affective	Impaired
							Affective First Order	Affective	Preserved
							Cognitive First Order	Cognitive	Preserved
							Affective Second Order	Affective	Impaired
							Cognitive Second Order	Cognitive	Impaired
Peron et al., 2010	13 PD 13 HC	Pre-DBS 53.3 (8.5)	Pre-DBS 10.5 (3.6)	Pre-DBS 1081.1 (605) Post-DBS 625.8 (600)	Pre-DBS 1.9 (0.9) Post-DBS 1.2 (1.0)	Pre-DBS 141.4 (1.7) on MDRS Post-DBS 141.1 (1.9) on MDRS	RME	Affective	Pre-DBS Preserved Post-DBS Impaired
Roca et al. 2010	36 PD (16 medicated 20 drug free) 35 HC	Medicated 63.4 (8.47) Drug free 63.5 (11.8)	Medicated 1.69 (1.55) Drug-free 1.23 (1.56)	Medicated 317 (256) Drug-free	Medicated 1.42 (0.57) Drug free 1.33 (0.54)	Medicated 29.00 (1.55) Drug free 28.26 (1.45)	RME	Affective	Preserved
							FPR	Cognitive and affective	Impaired cognitive component
							RME	Affective	Preserved
							FPR	Cognitive and affective	Impaired cognitive component

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.