Parkinson’s Disease: Clinical Profile and Social Cognition

Chapter 2

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Abstract

Social cognition is defined as a set of cognitive and emotional abilities which people use predominantly in social situations. Thus, it may be described as the array of mental processes involved in perceiving, remembering and processing information about social interactions. These processes enable us to understand oneself and others, control oneself and interact with others. A wide array of abilities is involved in social cognition, such as cognitive and affective Theory of Mind (ToM), empathy, and emotion regulation. Human social interaction relies on the ability to recognise and identify social cues as well as emotional cues such as facial expressions and prosody. Social cognition deficits have been tied to poor social competence, interpersonal functioning and communication.

Parkinson's disease (PD) is a progressive neurodegenerative disease associated mainly with the degeneration of dopamine neurons in the substantia nigra pars compacta. The pattern of degeneration starts from the dorsal striatum and then extends further to ventral parts when the disease progresses. In recent years a gradual modification of the definition of PD has been established, from a classical movement disorder to a multi-system neurodegenerative disease. Similarly the focus has shifted from motor symptoms to include a range of disabling non-motor symptoms such as sleep disturbances, cognitive decline, neuropsychiatric symptoms and autonomic dysfunction. Although highly disabling and impactful on quality of life, non-motor symptoms have only recently become the focus of medical treatment. Some studies have pointed out the existence of impairments of some social cognitive abilities in patients with PD. These studies have examined the relationship between dopaminergic pathways, social cognitive skills and cognitive decline with a particular emphasis on executive functioning. The results, although still not fully consistent, point to a dysfunction of some social cognitive skills. Given the impact of social cognition on the quality of life of patients with PD and possible implications

in the course of treatment, the aim of the present work is to examine evidence on impairment of social cognition in patients with PD.

Keywords: Social cognition, Parkinson's disease, Theory of Mind, Emotion recognition

Introduction

Clinical description

Parkinson's disease (PD) is a multisystem disorder associated with the aggregation of alpha-synuclein throughout the central, autonomic, and peripheral nervous system. PD is clinically characterised by motor and non-motor symptoms (NMS)[1], [2]. Primarily considered as a neurodegenerative disorder of the basal ganglia, it is accompanied by reduction of dopamine in both the caudate and putamen. Neocortex, particularly prefrontal areas, represent a main target of basal ganglion output by way of the thalamus: dopamine loss appears to be directly related to the presence and severity of motor symptoms and may result in frontal disconnections.

The typical motor symptoms of PD only allow diagnosis at a time point when approximately 60 to 80% of dopaminergic neurons in the substantia nigra have degenerated [3]. Cell loss is a widespread phenomenon that occurs in several brainstem nuclei: locus coeruleus (with noradrenergic projections to cortex), nuclei basalis of Meynert (which has a cholinergic input to cortex), substantia innominata, hypothalamus, mammillary bodies, mesencephalic reticular formation and dorsal raphe nucleus.

Clinical motor symptoms such as resting tremor, rigidity, bradykinesia and postural instability reflect the progressive degeneration of dopaminergic neurons projecting from the Substantia nigra pars compacta to striatal motor loci. An additional histopathological hallmark of the disease is the presence of intracytoplasmic inclusions called Lewy bodies found in the surviving dopamine neurons of the substantia nigra; the major component of these eosinophilic Lewy bodies are aggregated forms of the protein alpha-synuclein [4].

Although no environmental cause of PD has yet been proven, approximately 90% of cases (i.e. idiopathic Parkinson's disease) are presumably the consequence of a combination of genetic and environmental factors [5], [6].

Main motor and non-motor symptoms

Parkinson's disease is classically considered to be a prevalent motor system condition. There are four cardinal signs of PD: resting tremor, rigidity, bradykinesia and postural instability. In a clinical environment, the occurrence of any two of the first three signs is required to make a diagnosis. Postural instability is usually seen as a late sign, as it usually develops after several years. Onset of motor signs is typically asymmetric, as the most common initial finding can be an asymmetric resting tremor in an upper extremity. Over time patients develop worsening of motor functions, mainly related to progressive bradykinesia, rigidity and gait impairment. Furthermore, axial posture becomes progressively flexed and strides become shorter.

On the other hand, it is well recognized that PD patients can also show NMS, many of which precede motor dysfunction and represent a preclinical phase that may span several years [7]. NMS seem to be linked to a widespread distribution of alpha-synuclein pathology involving non-nigral brainstem nuclei, such as sympathetic and parasympathetic, enteric, cardiac and pelvic plexuses, and many other organs indicating a topographical and chronological spread, particularly in the prodromal stages of the disease [8].

Prior to diagnosis, a significant number of PD patients experience problems with olfaction, taste, nocturia, constipation, and cognitive impairment, which may help physicians to address a better differential diagnosis [9]. Patients with early PD[1] report a higher total number of NMS: among these, there is some evidence that early sleep disturbances occur in up to one-third of patients. According to the TREND study [3], early PD patients show more often hyposmia and rapid eye movement sleep behavior disorder, as well as a higher autonomic dysfunction score [11]. Furthermore, the presence of rapid eye movement sleep behavior disorder in PD has recently been associated with the development of PD dementia [12], [13].

[1] Excluding severe conditions of PD, i.e. Hoehn and Yahr Scale stages 4 and 5, according to the MDS Task Force Guidelines on the Hoehn and Yahr Scale, clinical stages can be defined as early on H&Y stages 1, 1.5 and 2, and moderate on H&Y stage 2.5 and 3 [10]

There is also growing literature reporting the frequency of neuropsychiatric symptoms (NPS), such as anxiety, depression, apathy, mental fatigue, psychosis, and impulse control disorders (ICDs) [14]–[18]. These NPS seem to be highly prevalent, affecting up to 60–80% of patients with PD [19]. Although NPS can occur in PD patients without dementia, cognitive impairment is a correlate of most of these disturbances and, as a whole, NPS are more frequent in patients with dementia. The most common NPS in PD patients with normal cognitive functioning are depression and anxiety, whereas apathy or lack of initiative and mental fatigue seem to be most frequent in PD patients with dementia. The most prevalent NPS seem to be those pertaining to the mood/apathy domain, followed by psychotic symptoms [17], [20].

Both neuropathological and pathophysiological backgrounds of NPS have been largely reviewed [15], [21]–[34]. Mood symptoms seem to be related to alterations in serotonergic pathways, a major target of anti-depressant medications. Serotonergic pathways are long known to interact with the dopaminergic degeneration associated with PD. Moreover, there is a reduction of grey matter densities in the orbitofrontal cortex involved in serotonergic pathways that may contribute to the onset of mood disorders [35], [36]. Lewy body lesions have been found in raphe nucleus in early stage of PD, further implicating a serotonergic pathology in PD depression [37]. Loss of adrenergic and serotonergic neurons may contribute to anxiety in PD [38].

Cognitive profile

The cognitive profile of patients with PD varies broadly between subjects and is also dependent on the duration of the disease [14], [30]. In PD there is a spectrum of cognitive dysfunction, ranging from mild cognitive impairment (MCI), i.e., a cognitive decline in the absence of dementia that is not normal for the age and educational level of the patient but with minimal effect on day-to-day functioning, to PD dementia [39]. The most commonly impaired domains

in PD-MCI appear to be executive functions and attention, as well as memory [40]. Additionally, a number of patients show a pattern of visuospatial dysfunctions.

Cognitive impairment in PD ranges from minor deficits, only demonstrable by means of comprehensive neuropsychological testing, to dementia. However, PD patients have a higher risk of developing cognitive dysfunctions. Moreover, PD patients with MCI seem to have an increased risk of developing dementia, both regarding frequency and rapidity of onset, than those without cognitive impairment [14], [16], [41]. The cumulative prevalence of dementia in PD is estimated as a minimum at 75% in patients surviving more than 10 years. Depression seems to be frequently associated with MCI in PD patients and seems to lead to a faster progression of cognitive decline. Disease severity and age appear to predict cognitive decline, in addition to cognitive reserve and genetic profile.

The neural underpinnings of cognitive impairment in PD are still a subject of debate and seem to result from a sum of heterogeneous mechanisms. Since PD is linked both to cortical Lewy pathology (in limbic and neocortical regions) and AD-related changes (in the hippocampus), cognitive decline may be associated with both PD and AD pathologies [42]. This translates in varying rates and degrees of damage to the major neurotransmitter systems in each individual.

PD-MCI has been differentiated into a relatively slow and a more rapid pattern of decline, respectively linked to frontostriatal deficits and posterior-cortical deficits. Early research on cognitive impairment in PD was mostly focused on the frontostriatal dysesecutive syndrome, which consists of deficits in planning, set shifting, working memory, response inhibition and attentional control. Impaired executive functioning in PD is linked to dopaminergic frontostriatal cortical loops. The relationship between dopamine levels and executive function in PD is multifaceted because of the specific sequence of degeneration of dopaminergic neurons within the Substantia nigra pars compacta. Whether or not executive

functions improve or deteriorate with dopaminergic stimulation depends on the advancement of degeneration within the Substantia nigra pars compacta. This complex relationship is explained by the 'dopamine overdose hypothesis', originally proposed by Gotham and colleagues in 1988, i.e., that cognitive tasks that rely on the ventral striatum will be impaired by dopaminergic medications in early PD because of overstimulation of the structure [43]. In addition, noradrenergic mechanisms likely contribute to reduced cognitive flexibility, by impairing set-shifting ability [30].

It has been argued that executive and attentional impairment may impact on the functioning of other cognitive domains, thus impairing memory, learning, visuospatial functions, and verbal fluency [44]. While this may be the case to some degree, studies on therapy naïve patients with early PD, showed memory deficits when executive functions were controlled for [45]. Moreover, hippocampal atrophy has been related to memory deficits in non-demented PD patients. Memory impairment may somewhat be determined by a pronounced Alzheimer pathology in a subgroup of patients. Nevertheless there is probably a considerable subgroup of patients with a more severe cholinergic deficit who also show a more temporo-posterior type of cognitive phenotype, with pronounced visuospatial deficits and more severe memory and language impairment, even in the relative absence of Alzheimer pathology (see [30] for a detailed review of the variety of cognitive domains that are impaired in PD and their biological underpinnings). Indeed, reduction in acetylcholine (Ach), triggered by the intrusion of Lewy bodies in the major ACh nuclei, is associated with attention deficits and may also play a role in changes in memory, language and visuospatial function. Bohnen and colleagues [46] in a carefully designed study, are among the first to suggest a possible cholinergic deficit related to olfactory dysfunction, a very early marker of PD, and cognitive functioning in non-demented PD patients. It has been recently proposed that this type of cognitive profile is distinct from the

more pure frontostriatal executive syndrome and is more strongly associated with development of a dementia syndrome resembling dementia with Lewy bodies (DLB) [47].

Pharmacological treatment

Heterogeneity in clinical presentation of PD patients represents a constant challenge for the physicians: treatment strategies depend on the patient's age, disease stage, most troublesome symptoms, the balance between efficacy and risk for each treatment option. However, it is important to base treatment decisions on the best available data for each intervention. It is well established that a patient's quality of life deteriorates quickly if treatment is not instituted at or shortly after diagnosis [48].

Pharmacologic treatment of PD can be generically divided into symptomatic and neuroprotective (or *disease modifying*) therapy. Neuroprotective therapy aims to slow, block, or reverse disease progression; such therapies are defined as those that slow underlying loss of dopamine neurons. At this time, there is no proven neuroprotective therapy, although there remains interest in the long-term effects of monoamine oxidase (MAO)-B inhibitors. .

As for symptomatic therapy, Levodopa, coupled with a peripheral decarboxylase inhibitor, remains the gold standard of treatment for Parkinson disease. Levodopa provides the greatest antiparkinsonian benefit for typical motor signs and symptoms, with the fewest adverse effects in the short term. Initial treatment of early disease stages may benefit of MAO-B inhibitors (such as rasagiline and selegiline), as they can provide mild symptomatic benefit, have excellent adverse effect profiles, and, according to a Cochrane review, have improved long-term outcomes in quality-of-life indicators by 20-25% [49].

Dopamine agonists such as ropinirole, pramipexole, rotigotine provide moderate symptomatic benefit and delay the development of motor complications such as dyskinesia. A review of the Cochrane and PubMed databases from 1990 to 2008 found that these agents

caused a 15% increase in adverse events such as somnolence, sudden-onset sleep, hallucinations, oedema, and impulse control disorders (eg, pathologic gambling, shopping, and Internet use; hypersexuality; and hoarding) [50]. More recently, new agents like Safinamide (a mixed MAO-B inhibitor and Glutamate release inhibitor) have been proposed as an add-on therapy to dopamine agonist therapy in both early and advanced PD [51].

Over time, symptomatic therapy for late disease requires different strategies: such medications usually provide good control of motor signs of PD for 4-6 years. Despite best medical management, disability often progresses and many patients develop long-term motor complications, including fluctuations and dyskinesia. Additional causes of disability in advanced disease include postural instability (balance difficulty) and dementia.

Another aspect worth mentioning is that dopamine therapy has been related to impulsive/compulsive behaviours (ICBs) as an iatrogenic complication. ICBs consist of dopamine dysregulation syndrome (DDS), punding, and ICDs [52]–[56]. Dopamine dysregulation syndrome is characterized by a bizarre phenomenon of an ineffectiveness of medications during "off" periods and occurs mostly due to compulsive overuse of dopaminergic treatment, resulting in secondary cognitive and behavioural disturbances [54], [55]. The main subtypes of ICDs include pathological gambling, hypersexuality, compulsive eating and shopping [52], [56]. ICDs are considered separately given their proven association with dopamine agonists in multiple case control studies [52], [57], [58], as compared with DDS, which seems to be more closely associated with levodopa [59], and punding, whose association with levodopa or dopamine agonists is not yet clear [60]–[62].

Personality traits related to impulsivity and sensation seeking are associated with drug dependence, drug craving, and vulnerability to relapse. They also play a prominent role in the development of DDS [63]. Besides, disruption of the reciprocal loops between the striatum and

structures in the prefrontal cortex following dopamine depletion are likely to predispose to DDS [63].

Continuous jejunal levodopa infusion might have positive effects on DDS, ICDs, and punding as well as motor complications in PD patients [64]–[68]. However, it can not be considered useful in every instance because there is some evidence that it may trigger behavioural abnormalities in sensitive PD patients [69].

It is a common strategy to emphasise on long-term considerations to guide early treatment in younger patients, due to the higher chance of developing motor fluctuations during a lifespan. On the other hand, older patients, particularly those with cognitive impairment, are treated with a main focus on providing adequate symptomatic benefit in the near term, with as few adverse effects as possible.

Pharmacological treatment of non-motor symptoms

An evidence-based guideline from the American Academy of Neurology reports that physician's recognition of depression is considerably low in Parkinson disease, at less than 30% of clinically proven cases. There are many factors that concur in a delayed diagnosis, even considering that depression has the single largest effect on the quality of life of patients with PD [70], [71].

Dopaminergic neurotransmission is affected in non-PD depression, and antidepressants act in part by increasing nucleus accumbens' dopamine receptor sensitivity [72]. Dopamine enhancement therapies, including the MAO-B inhibitor selegiline [73], [74] and the D2/3 agonist pramipexole, are effective in treating major depressive disorder in the general population [75], [76].

Striatal and extrastriatal dopaminergic pathways have been implicated in the pathogenesis of depression and other NMSs in PD [72]. Several papers report that dopaminergic

medications can improve depression and other NMSs in PD. Levodopa may improve depression in PD, although the literature is limited and focused on patients with motor fluctuations [77], [78]. Pramipexole improved depressive symptoms in patients with PD in a placebo-controlled study [79]. Examination of MAO-B inhibitors for the treatment of depression in PD is limited.

Dopamine-enhancing therapies may also improve cognitive symptoms in PD. Levodopa plays a role in executive dysfunction, due to its modulation of the parallel dopaminergic pathways that connect the cortex and basal ganglia [80]. Rasagiline may improve attention and verbal fluency in patients with PD and MCI [81]. In addition, catechol-*O*-methyltransferase polymorphisms that increase dopamine levels in the prefrontal cortex correlate with better executive abilities and neuroimaging studies have reported a correlation between nigro-caudate dopamine impairment and executive dysfunction and future cognitive decline [82].

Social cognition in Parkinson's Disease

Definitions and models

Social cognition has been generally defined as the ability to identify, perceive, and interpret socially relevant information, in order to generate an appropriate and adaptive response [83]. Social-cognitive skills are comprised by a broad set of mental processes that underlie social interactions. They are linked to modulating both automatic and volitional behaviour with responses to socially relevant stimuli by recruiting memory, decision-making, attention and motivation. Social cognitive performance is a result of a set of skills that plays a significant role in successful interpersonal functioning. These skills have been known to be impaired in several neurologic diseases [84].

Although social cognition has been studied for many years, there are large differences in the terminology and the theoretical models used to explain it. This fact is probably due to the

multifaceted character of social cognition, which is composed of a set of multi-factorial constructs that encompass multiple sub-processes [85], in particular Theory of Mind (ToM), empathy, and emotion perception.

One of the key dimensions among the social cognitive processes affected in PD is ToM, defined as the ability to infer and predict other people's intentions, beliefs, thoughts and desires in order to understand and explain their behaviour [86]. This ability requires the awareness that others have a mind with mental states that may differ from our own. Therefore, ToM is a broad term that incudes different abilities: namely the ability to represent cognitive and affective mental states, the ability to attribute these mental states to one's self or others and to deploy these mental states in order to understand and predict behaviour. Findings from lesion studies suggest that prefrontal and frontal brain areas play a key role in ToM abilities [87], [88]. Furthermore, findings from neuroimaging studies suggest the existence of a distributed neural network that underlies ToM abilities. This network is likely comprised of the posterior superior temporal sulci (pSTS), the adjacent temporo-parietal junctions (TPJ) areas, the precuneus, and the prefrontal cortex (PFC) (especially its medial portions) [89]–[91].

A model proposed by Shamay-Tsoory and colleagues [92], [93] divide ToM in two separate systems, namely cognitive ToM and affective ToM. Cognitive ToM is described as involved in processing inferences about others' beliefs and intentions, whereas affective ToM is involved in processing inferences about other people's emotions and feelings. While cognitive ToM is thought to require understanding of the difference between the speaker's knowledge and that of the listener, affective ToM seems to also require an empathic appreciation of the listener's emotional state. A model of affective and cognitive ToM describing common and diferrent brain areas involved has been proposed by Poletti, Enrici, and Adenzato [84] (see Figure 1).

Figure 1 about here

As for social cognition, ToM is also considered a multidimensional construct, with distinctive subcomponents that are differently recruited by ToM tasks (e.g., false-beliefs tasks for cognitive ToM and the Reading the Mind in the Eyes task for affective ToM respectively, see below). The literature links affective ToM with lesions of the ventromedial PFC. On the other hand, given the more complex set of skills required for cognitive ToM, its neural substrates are less documented and more controversial. Some models suggest the involvement of the dorsolateral PFC in cognitive ToM [93]. Recent findings indicate that the posterior regions of the ToM network (i.e. the precuneus, TPJ, and pSTS) might play a major role in assigning agency to mental states [94] instead of exhibiting a preference for the processing of cognitive or affective mental states. Thus, recently the traditional distinction between cognitive and affective processes has been questioned by growing evidence that several structures play a prominent role in both functions.

Another crucial dimensions of social cognition is empathy, defined as the complex ability to recognize the emotions and feelings of others, with a minimal distinction between self and other [95]. In a comprehensive model of human empathy, Decety decomposes the construct of empathy in three different subcomponents [95]. The author argues that these components, namely affective arousal, emotion understanding and emotion regulation, are a part of a network of distributed, often recursively connected neural regions (including the STS, insula, medial PFC, ventromedial PFC, amygdala and anterior cingulate cortex). These regions, together with

endocrine and autonomic processes, seem to be implicated in social behaviours and emotional states. Indeed the perception and the experiencing of emotions may be affected by goals, intentions, context and motivations, thus requiring a complex network in order to process and respond to emotional stimuli. The author posits that the first component of empathy, namely *affective arousal*, develops at birth and serves the purpose of differentiating hospitable from hostile stimuli. Affective arousal is mainly composed by subcortical circuits (amygdala, hypothalamus, hippocampus and orbital frontal cortex) connected to the STS that allow rapid and prioritised processing of the emotional signal. *Emotion understanding* develops later and matures around the age of 2-3 years. It largely overlaps with ToM-like processing and is closely linked to executive functions, likely involving ventromedial PFC, medial PFC. On the other hand *emotion regulation* consists of the ability to control emotion, affect, drive and motivation. It involves networks that connect dorsolateral PFC, anterior cingulate cortex, ventromedial PFC with the amygdala and widespread cortical areas including the STS. Emotion regulation develops throughout adolescence, paralleling the development of executive functions.

Finally, another important component of social cognition affected in PD is emotion perception. Recently Mitchell and Phillips [85] have described a model that links ToM and emotion perception define as a set of skills that allows the identification of emotionally salient information in the environment. This information consists of verbal (lexico-semantic) and non-verbal (prosody, facial expressions, body movement) cues that are used for the perception of the emotions displayed by others. This model integrates what was previously referred to as 'hot' and 'cold' social cognition with models that refer to the level of processing of social information (perceptual representation vs. reasoning about social information). By analysing different studies the authors suggest that both emotion perception and ToM are right-hemisphere based and share the activation of overlapping regions, namely the medial PFC and temporal lobe areas. They posit that ToM requires temporal-cingulate networks, while emotion perception

involves partially segregate regions linked to different emotions and that differences in activation also depend on perceptual, cognitive and emotional demands on emotion perception and ToM tasks.

Theory of mind impairment in Parkinson's disease

Research on ToM in PD has proposed different hypotheses of the possible mechanisms responsible for the impairment of this domain. Bodden and colleagues [96] have proposed three different sets of arguments for ToM impairment associated with basal ganglia dysfunction. Firstly, the neuropsychological argument refers to the frequently observed association between cognitive impairment of domains related to ToM. The neuroanatomical argument points to the importance of the basal ganglia in the frontostriatal circuitry, comprised of both the frontal lobe and limbic structures, important for ToM related functions. The neurophysiological argument accounts for the possible connection between social cognition and the dopaminergic system.

Regarding the neuropsychological argument the authors examine the connection between executive functions and ToM abilities, which, although functionally dissociated, seem to be in some way linked. Executive functions have indeed been conceptualised as a co-opted system parallel to a core ToM system, required for at least some ToM tasks. Given the role of the basal ganglia in executive functioning, it can be speculated that executive dysfunction may determine a decrease in performance on ToM tasks [97]. On the other hand, the neuroanatomical argument examines the crucial role of the substantia nigra in the frontostriatal pathways that mediate ToM functions and other complex behaviours [96]. Specifically, the frontostriatal pathways seem to be involved in emotional aspects of behaviour (via orbitofrontal-limbic-striatal circuits) as well as in executive aspects of behaviour (via dorsolateral-prefrontal-striatal circuits). This division, although oversimplified, reflects the abovementioned conceptual distinction of hot and cold components in social cognition. Finally,

the neurophysiological argument originates form the hypothesis that dopaminergic and serotonergic dysfunction may cause impairments in ToM [98]. Supposedly dopaminergic and serotonergic systems innervate neuroanatomical regions crucial to ToM (PFC, TPJ, anterior cingulate cortex) and play a role in cognitive functioning (e.g., executive functions and language). Moreover, the dopaminergic system is involved in complex behaviours, such as the evaluation of the consequences of future events and actions, ability closely related to ToM.

A recent meta-analysis [99] examined the growing literature on ToM in PD. The authors analyse the differences among studies, in order to clarify which particular aspects of ToM are impaired. The authors examined modality, i.e., verbal vs. visual, content, i.e., inferring beliefs and motivations (cognitive) vs. inferring what a person is feeling (affective), and complexity, (i.e., basic vs. complex, of stimuli used in previous studies in this domain. The authors found consistent evidence of ToM impairment in PD, which manifests in early stages of the disease and may become more severe in later stages of the disease. Moreover, given that the meta-analysis only included patients with mild or moderate stages of disease severity, the authors argue that the cortical diffusion of Lewy bodies may lead to more severe ToM impairment in advanced stages. They found no evidence of significant differences comparing presentation modalities (visual vs. verbal). Also the severity of ToM impairment seems to be correlated to executive functioning and verbal fluency. ToM deficits were present in both cognitive and affective tasks, but were prominent in cognitive ToM, at least in early stages. This finding may indicate a predominant involvement of the dorsolateral fronto-striatal network in early stages, which progresses to ventromedial/limbic fronto-striatal circuits in advanced PD. This progression of the affected networks may explain the negative findings of affective ToM tasks in studies with early PD patients. Indeed patients with early PD seem to perform comparably to healthy controls; while patients in more advanced stages initially develop cognitive ToM deficits, which are accompanied by impairment of affective ToM components in more advanced

stages of disease. Therefore, ToM dysfunctions occur in PD and are aggravated throughout the progression of the disease.

Different tasks have been used to explore ToM in PD. The Reading the Mind in the Eyes (RME) test has been the primary task used by authors to assess affective ToM in PD (emotion representation), consisting of the presentation of photographs of the eye region of human faces. 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). Although the results are not fully consistent, they suggest that affective ToM seems to be impaired at later stages of the disease, but may be also impaired in early stages [100], [101]. Santangelo and colleagues [102] used a different task to assess affective and cognitive ToM yielding similar results and suggesting that both components may be impaired in early PD.

In the Faux pas 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. 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, faux pas test was designed to differentially assess both the cognitive and affective aspects of ToM. Faux pas recognition tasks seem to indicate an impaired performance to the cognitive component of the task and a preserved performance to the affective component [103]. This means that PD patients were able to detect inappropriate remarks in the stories but found it difficult to infer the reason why the person had made the inappropriate remark [104], [105].

The ability to infer other's beliefs has been assessed by some studies indicating probable impairment of cognitive ToM [106]–[108]. The nature of this impairment varies between studies probably due to differences in patient selection criteria. This task is comprised by two tests (first and second-order false belief). The first-order belief test assesses the ability to infer someone's mistaken belief about the world (e.g. someone's belief about the location of an object) that is different form the subject's own true belief. The second-order false belief test is a more complex task that requires the ability to form beliefs about mental states. Indeed the subject is required to form beliefs about someone else's beliefs (e.g. B's beliefs about A's beliefs about the location of an object). Furthermore, PD patients seem to have lower performances on the second-order affective component and in the second-order cognitive component of the Yoni test [109].

Additionally some studies had addressed abilities that may be linked to ToM components. For example, McNamara and Durso [110] found a decrease in pragmatic language abilities in PD. Particularly, the authors observed impairments in the areas of conversational appropriateness, turn-taking, prosodics and proxemics, related to frontal lobe dysfunction. Moreover, Berg and colleagues [111] have described an impairment in the ability to process implied information, suggesting a difficulty in making inferences.

Emotion recognition in PD

A growing literature points to the existence of a disturbance in the recognition of facial emotion expressions in PD patients [112], [113]. As of now results seem inconsistent, even though most studies have found a decreased ability to recognise facial expressions of emotions. Authors usually employ two kinds of tasks in order to assess emotion perception and recognition. The first kind of tasks are discrimination tasks, in which the subject is asked to judge whether two facial expressions are similar or different. These tasks require the ability to explore the two

stimuli and the relevant details of each expression in order to evaluate their similarities. Visuospatial abilities as well as perceptual abilities have to be preserved in order to carry on such analysis.

The majority of studies on emotion recognition in PD have employed identification tasks. These types of tasks require the subject to attribute a linguistic label to a facial expression of emotion. In order to do this the subject has to link the facial expression to its affective meaning, which may require executive abilities such as working memory, attention, decision-making and categorisation [114].

The results of the bulk of studies on emotion recognition in PD point to the existence of a deficit in emotion recognition (see table 1 and 2). While a group of studies found impairment in specific emotions (i.e. disgust, fear, anger, surprise, see table 2), a second group of studies found a generalised decrease in the ability to identify and recognise emotional facial expressions (see table 1). A different group of studies found no impairment of emotion recognition abilities in PD (see table 3).

Tables 1, 2, and 3 about here

Conclusion

A growing literature suggests the existence of deficits of social cognition in PD patients, although these finding are still debated [84], [136]. The limitations of many studies lay in the multifaceted nature of social cognitive skills. Indeed studies have to dissect a highly interactive set of different skills in order to pinpoint a selective impairment. This task is very complex, given the limitations of scientific methodology on the study of such intricate abilities. Despite

such difficulties, social cognitive abilities, as a crucial prerequisite for social human interaction, are highly relevant for various types of social situations [137]. Decoding and attributing mental states as intentions and emotions of a communicative partner enables and deepens social relationships by aiding positive and empathic communication. Additionally the understanding of complex communicative intentions is a prerequisite of empathic and effective communication skills. Thus, impairments of social cognition can have repercussions on neurological and psychiatric symptoms therefore determining a vast impact on a patient's life. Social cognitive deficits have clinical significance since interpersonal difficulties are common in PD and, in many cases, even more damaging to quality of life than motor symptoms. Additionally, there are several potential sources of interpersonal difficulty in PD, including the common tendency to mistake the symptoms of PD, such as loss of facial expression due to rigidity of facial muscles, as indicators of negative personality traits.

The future development of social cognition studies has to pursue a course of treatment for PD patients, as a way to intervene in this potential vicious cycle. In order to do this, patients with PD could be provided with specific training in emotion recognition, as well as in cognitive and affective components of ToM. The first step may be to educate and inform PD patients and their caregivers about the implications of emotion recognition and representation difficulties and associated consequences. Future development may also include the adaptation of psychotherapeutic approaches for the treatment of patients with PD who suffer from social cognition dysfunctions.

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Table 1: Studies including a generalised impairment in emotion recognition. The order is chronological.

Authors	Sample	Emotions	Experimental tasks	Presentation time	Results
Beatty et al., 1989 [115]	43 PD 27 HC	Happiness, sadness, anger, fear, disgust, surprise, neutral	110 faces from Ekman and Friesen	No time	Generalised impairment in emotion recognition
Jacobs et al., 1995 [116]	12 PD 30 HC	Happiness, sadness, anger, fear and neutral	Subtest 1, 2, 5 form FAB-r (facial identity discrimination and facial affect identification and matching	--	Impairment in perceiving emotional faces
Breitenstein et al., 1998 [117]	14 PD 32 controls with focal cortical lesions	Happiness, sadness, anger, fear and neutral	Tübingen Affect Battery (facial expressions)	--	Impairment of emotion recognition in advanced PD and no impairment in early PD
Yip et al., 2003 [118]	64 PD 64 HC	Happiness, sadness, anger, fear surprise and neutral	Japanese and Caucasian Facial Expressions of Emotion (JACFEE) compilation: identification and discrimination tasks	10 seconds	Generalised emotion recognition impairment Bilateral PD: impaired recognition, especially fear and sadness; right-sided: impaired recognition for sadness and disgust and no impairment for happiness
Dujardin et al., 2004 [119]	18 PD 18 HC	Anger, disgust, sadness, fear	Emotional facial expression decoding (Hess and Blairy, 1995) rate emotion and quantify intensity	No time limits for recognition	PD patients were significantly impaired in decoding EFEs, as well as in executive function.
Herrera et al., 2011 [120]	40 PD 19 HC	Happiness, sadness, anger, fear, surprise and disgust	Emotion categorisation of faces selected from MacBrain Face Stimulus Set	--	Facial emotion recognition deficit in PD patients after controlling for demographic and cognitive characteristics of the participants.
Enrici et al., 2015 [121]	32 PD 25 HC	Happiness, sadness, anger, fear, surprise and disgust	Ekman 60-Faces	No time limits for recognition	Generalised impairment in emotion recognition; no correlation with dopamine

	therapy, disease severity or duration of illness

Table 2. Studies including a specific impairment in emotion recognition. The order is chronological.

Authors	Sample	Emotions	Experimental tasks	Presentation time	Results
Kan et al., 2002 [122]	18 PD 24 HC	Dynamic: Happiness, sadness, anger, fear surprise, disgust Static: Happiness, disgust, anger, sadness, neutral	Dynamic facial expression recognition; recognition of static facial expressions	2 conditions: no time limit and 2 sec.	Impairment in the recognition of fear and disgust
Sprengelmeyer et al., 2003 [123]	16 unmedicated PD 20 medicated PD 40 HC	Happiness, sadness, anger, fear, surprise and disgust	Ekman 60 Faces Test	3 seconds	Impaired recognition in both PD groups (greater deficits in unmedicated PD especially for disgust)
Lachenal-Chevallet et al., 2006 [124]	12 PD 14 HC	Happiness, fear, anger, disgust, neutral	Emotion recognition task with morphed faces	--	Impairment in recognition of fear and disgust
Suzuki et al., 2006 [125]	14 PD 39 HC	Happiness, sadness, anger, fear, surprise and disgust	Sensitivity to basic facial emotions in 72 facial stimuli (12 prototypical basic emotions and 60 coupled morphed images	Unspecified	Impairment in recognition of disgust
Lawrence et al., 2007 [126]	17 PD 21 HC	Happiness, sadness, anger, fear, surprise and disgust	Ekman 60 Faces Test	No time limits for recognition	Impairment in recognition of anger
Ariatti et al., 2008 [127]	27 PD 68 HC	Happiness, sadness, anger, fear, surprise and disgust	Facial emotion recognition battery (Ekman and Friesen) Facial affect naming, selection and matching tasks	Unspecified	Impairment in recognition of sadness and fear

Martins et al., 2008 [128]	17 PD 20 HC	Happiness, fear, sadness, anger, surprise	Basic emotion recognition task	500ms for presentation, 1000ms for answer	Impairment in recognition of fear and anger
Clark et al., 2008 [129]	20 PD 23 HC	Happiness, sadness, anger, fear, surprise, disgust, neutral	Facial emotion recognition (Ekman and Friesen)	No time limits for recognition	Impairment in recognition of surprise and anger
Assogna et al., 2010 [130]	70 PD 70 HC	Happiness, sadness, anger, fear, surprise and disgust	Penn Emotion Recognition Test	No time limit	Impairment in recognition of disgust related to some neuropsychological measures
Martinez-Corral et al., 2010 [131]	31 PD (12 apathy and 19 non apathy) 16 HC	Happiness, sadness, anger, fear, surprise and disgust	Emotion identification from FERT (JACFEE)	3 seconds for presentation; no time limit for answer	Impairment in recognition of fear, anger and sadness in patients with apathy; no impairment in patients without apathy
Clark et al., 2010 [132]	16 PD 20 HC	Happiness, sadness, anger, fear, surprise, disgust, neutral	Facial emotion recognition battery (Ekman and Friesen)	No time limits for viewing	Impairment in recognition of surprise in right sided paients and anger in left sided patients

Table 3. Studies including no impairment in emotion recognition. The order is chronological.

Authors	Sample	Emotions	Experimental tasks	Presentation time	Results
Adolphs et al., 1998 [133]	18 PH 13 HC	Anger, surprise, happiness, fear, sadness, disgust, neutral	Facial emotion recognition battery (Ekman and Friesen)	No time limits for recognition	Intact recognition of facial emotions
Pell, Leonard, 2005 [134]	21 PD 21 HC	Happiness, surprise, anger, disgust, sadness	Discrimination, naming and rating of basic emotions	Unspecified	No significant impairment
Ille et al., 2016 [135]	25 PD 25 HC	Fear, Anger, Disgust	Recognition and intensity of 30 pictures from the Karolinska set	15 seconds	Intact emotion recognition and experience (but dysfunctional emotion regulation)

Figure 1

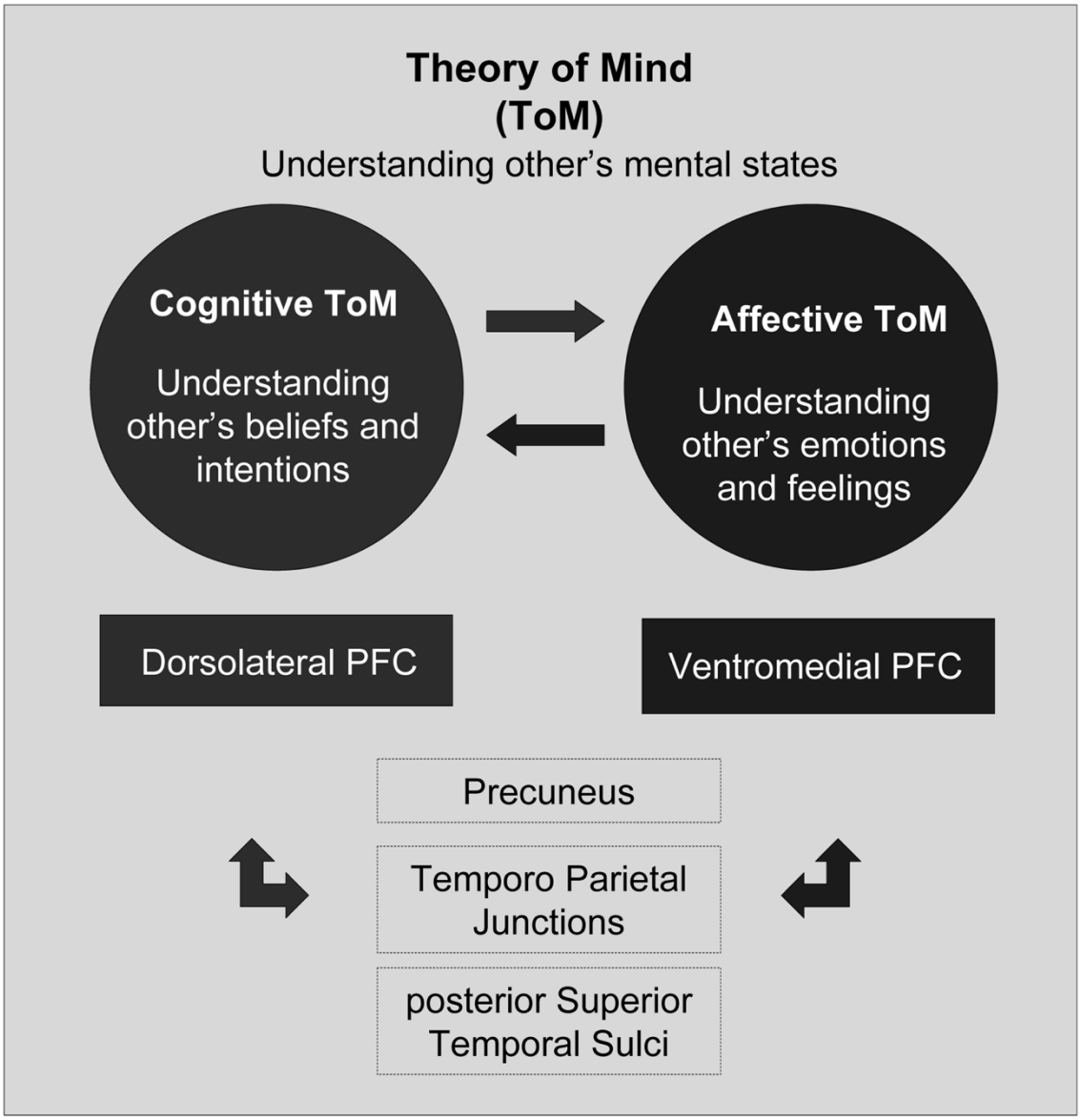
Theory of Mind
(ToM)
Understanding other's mental states
Cognitive ToM
Understanding other's beliefs and intentions
Affective ToM
Understanding other's emotions and feelings
Dorsolateral PFC
Ventromedial PFC
Precuneus
Temporo Parietal Junctions
posterior Superior Temporal Sulci

Figure Captions

Figure 1. A model of ToM comprised by the affective and cognitive component with common and different brain areas involved. Reprinted with permission from Poletti and colleagues [84].