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Abstract

Introduction: Growing evidence highlighting a social cognition (SC) deficit in Parkinson's disease (PD) have recently emerged, while pointing to ambiguous findings. Our objective was to determine if SC abilities impairment is frequent at the early stages of PD.

Methods: 109 patients with idiopathic PD diagnosed within the past four years (ICEBERG cohort) and 39 healthy participants were enrolled in this study. SC was evaluated using the Mini-Social Cognition and Emotional Assessment (Mini-SEA), that allows a multi-domain assessment of SC. Relationships between SC and clinical characteristics, global cognitive efficiency, mood, anxiety, apathy and impulse control disorders, were also evaluated.

Results: 30% of the cohort of patients was significantly impaired on the socio-emotional assessment. Further, SC deficit in isolation (20.2% of the cohort) was 3.5 times more frequent than a Mild Cognitive Impairment in isolation (5.5%). Both emotion identification and Theory of Mind were impaired compared to healthy participants. No effect of age, level of education, disease severity or dopamine replacement therapy, and global cognitive efficiency were found. Only scores on the Frontal Assessment Battery were correlated with the SC abilities.

Conclusion: SC impairment is frequent in early PD and should be given more consideration. It is commonly observed in the absence of any other cognitive disorder and may represent the most common neuropsychological deficit at the early stages of PD. In line with the definition of MCI criteria, we suggest highlighting the presence of a sixth MCI subtype and naming it the "Mild Social Cognition Impairment (MSCI)".

Introduction

Early signs of Parkinson's disease (PD) have been the focus of increasing attention over the past decade, including cognitive, but also behavioural and emotional aspects. Cognitive deficits in PD classically affect executive functions, attention, processing speed, and visuo-spatial functions[1], which are mainly assigned to a striato-frontal axis dysfunction, although a second profile related to a more posterior cortical dysfunction has been identified[2]. The Movement Disorder Society (MDS) recently defined the Mild Cognitive Impairment criteria in PD (PD-MCI)[3], knowing as a cognitive decline compared to the premorbid functioning which is not severe enough to significantly disrupt daily living. Five subtypes of PD-MCI had been proposed according to the following cognitive domains: attention and working memory, executive functions, visuospatial skills, memory and language[3]. PD-MCI is common, affecting 20-50% of patients[3,4], already at the time of PD diagnosis. It is known as a strong predictor of dementia[3,4] and contributes to poor quality of life[4].

Social cognition (SC) is a less explored field at the early stage of PD. SC refers to how people process, store, and apply information regarding interpersonal relationships and complex social interactions[5,6]. It relies on emotional processes, as well as other higher-order functions, such as awareness of other's thoughts and intentions, social problem-solving abilities, understanding metaphor, humour and sarcasms, or making moral decisions[6]. Emotional processes include basic emotion perception (happiness, fear, anger, disgust, surprise, sadness), which can be triggered by facial expressions, voice prosody or body postures. Emotional processes also involve comprehension of more socially complex emotions (guilt, shame, embarrassment, jealousy, pride…) and empathic feelings. The ability to infer other people's mental states, such as beliefs, desires and intentions, is known as Theory of Mind (ToM)[7–11]. ToM is built upon a cognitive part that allows attribution of

beliefs, intentions and motivations to others, and an affective part that implies the understanding of other's emotions and feelings[12]. The ability to decipher and respond to the emotional content and social conventions present in the environment is crucial for successful interpersonal relationships and impacts the quality of life.

Most studies that investigate emotional processes in non-demented PD patients reported impaired recognition of negative emotions, mainly fear, anger and disgust, from facial expression, as well as body gestures or prosody decoding[6,13–16]. Meta-analytic reviews regarding ToM abilities showed an impairment that mainly affects cognitive part and became more severe as the disease progresses[7–9]. Findings are less consensual regarding whether the affective component is impaired[9–12] or not[8,17]. In addition, decreased cognitive empathy, lack of understanding of humour and irony, as well as more egoistic morality dilemma choices have been also found in non-demented PD patients[6,18].

To date, the questions whether social cognitive appears as an early symptom[9,11,17,19-21] and to what extent affective and cognitive components are each affected are still debated[9-12]. Moreover, there is conflicting evidence regarding relationships with other cognitive functions[9,11–13,17,19,21], mood[11,13,14] and behavior[20], treatment[13,17,19] and motor severity[8,12–14,17,18].

In this study, we examined a multidomain social cognition task in a large population-based cohort of newly diagnosed PD patients with or without MCI to clear up the social cognitive impairment in PD. Our main predictions were: 1) Impairment of social cognition abilities is an early symptom of PD; 2) Impairment of social cognition abilities is frequent in PD; 3) Several domains of social cognition are affected; 4) The social cognitive deficit represents a symptom by itself which is independent from other motor, cognitive and behavioral impairments.

Methods

Participants

We recruited 109 PD patients diagnosed according to the MDS clinical diagnosis criteria and 39 healthy controls (HC) from November 2014 to June 2018 (ICEBERG cohort study clinicaltrials.gov, NCT02305147). This cohort included patients with PD diagnosed within the past four years at inclusion and excluded patients with Scans without Evidence of Dopaminergic Deficit (SWEDD), atypical Parkinson syndromes, or those currently taking neuroleptics or having taken them within the last six months prior to inclusion. Non-inclusion criteria for all participants were presence of dementia or severe cognitive impairment (MMSE $\leq$ 26/30), and history of neurological or psychiatric disorders. PD patients were administered their daily optimal dopamine replacement therapy and were evaluated while in their ON condition. The study was conducted at the Clinical Investigation Centre in the Neurology Department of Pitié-Salpêtrière Hospital. ICEBERG study was sponsored by Inserm and was conducted according to good clinical practice. It received approval the local Ethics Committee (RCB: 2014-A00725-42) and all subjects signed informed-consent prior to investigation.

Clinical and experimental assessments

Clinical assessment

Motor severity was evaluating using the MDS-UPDRS part III[22] and Hoehn & Yahr staging scale. L-dopa equivalent daily dose (LEDD) and dopaminergic agonist daily dose were calculated. Global severity of the disease was evaluated with the Clinical Global Impression scale (CGI).

The neuropsychological battery included two general cognitive efficiency scales recommended by MDS guidelines[3], the Montreal Cognitive Assessment (MoCA)[23] and the Mattis Dementia Rating Scale[1], and a global evaluation of executive functions with the

Frontal Assessment Battery[1]. Mood and anxiety were assessed by the Hospital Anxiety and Depression scale (HADS). Behavioral disorders were investigated using the part III of Ardouin Scale of Behavior in PD (ASBPD)[24] for Impulse Control Disorders (ICD) and the Starkstein Apathy Scale (SAS).

The Mini-Social Cognition and Emotional Assessment (Mini-SEA)

Social cognition was evaluated using the Mini-Social Cognition and Emotional Assessment (Mini-SEA)[25,26] . The Mini-SEA is an abbreviated version of the SEA[25], that allows a multidomain assessment of social cognition. Mini-SEA includes two subtests measuring emotional identification, through a facial emotion recognition test based on the Ekman pictures sample, and ToM abilities, using a shortened version of the "Faux-Pas" Recognition test.

Emotion Identification Test

Participants had to identify which emotion was expressed on a face picture out of six primary emotions (fear, sadness, disgust, surprise, anger, happiness) and a neutral expression. The choices stayed constantly displayed on the screen. Each emotion was presented five times. A total score out of 35 was obtained, as well as a calculated score out of 15[25]. We distinguished between a total positive (happiness) emotion score (out of 5) and a negative (fear, sadness, disgust, anger) emotions score (out of 20).

ToM Test

This subtest included five stories described as "faux-pas", i.e. an embarrassing or tactless act or remark made unintentionally by someone in a social situation, and five control stories. To reduce memory load, participants were read the stories while a written version was also placed in front of them. After each story, participants were asked if something inappropriate was said (Faux-Pas detection). If they answered positively, further clarifying questions were

proposed in order to test their understanding of the « faux pas » situation: four questions about the cold understanding (attribution, intention, inference, understanding) and one question about the feelings of the protagonist. Finally, patients were asked two control questions to verify their comprehension (out of 20). Total score was the sum of correct responses for « faux pas » stories (out of 30). Two complementary sub scores were calculated: a « cognitive ToM » score that results from the sum of the first five questions (out of 25) and an « affective ToM » score that refers to the last question (out of 5).

Neuropsychological Profile Classification

According to the MDS PD-MCI level 1 criteria[3], the MoCA was chosen to determine if the participants were cognitively impaired: subjects with a score under 26 out of 30 on the MoCA[23] were categorized as "MCI". A cut-off score of 23.1 was established for the Mini-SEA, which corresponds to 1.5 SD above the mean following the definition of MDS-MCI recommendation[3] : subjects with a score under 23.1 out of 30 on the Mini-SEA were classified as presenting Social Cognition impairment (SCI). All participants were classified into four sub-groups based on the preservation or impairment of their cognitive and socio-emotional functioning: "no MCI/no SCI" if MoCA $\geq$ 26/30 and Mini-SEA $\geq$ 23.1/30, "MCI/no SCI" if MoCA < 26/30 and Mini-SEA $\geq$ 23.1/30, "no MCI/SCI" if MoCA $\geq$ 26/30 and Mini-SEA < 23.1/30, and "MCI/SCI" if MoCA < 26/30 and Mini-SEA < 23.1/30.

Statistical analysis

Demographic, clinical, and neuropsychological measures were compared between PD patients and HC using Chi-squared test for categorical variables and t-test for continuous variables. To compare the distribution of MCI groups between PD patients and HC, a Chi-squared test was done. Linear regressions were performed to study the impact of clinical

group (PD patients vs HC) adjusted for gender, age, education, HAD anxiety, HAD depression and Starkstein Apathy Scale on SC based on total Mini-SEA score, identification of emotions total score, identification of positive emotions score, identification of negative emotions score, « faux pas » score, cognitive ToM score and affective ToM score. Corrections for multiple comparisons were performed using the Benjamini-Hochberg method. The same steps were applied when studying the impact of several effects on SC in PD patients. The same effects as the previous analysis comparing PD patients and HC were added in the linear regressions, except group effect and adding FAB, MMSE, MDS UPDRS OFF, LEDD and ICD. For all linear regressions, Cohen's f2 were calculated to assess effect sizes. Normality of residuals and heteroskedasticity were checked visually. Cook's distances and hat values were computed to investigate potential influencers and outliers. Statistical analyses were performed using R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.)

Results

Demographic and clinical assessments

Demographic, clinical, and neuropsychological characteristics of PD patients and HC are shown in Table 1. Groups did not differ for demographic variables such as age and level of education. The gender proportion was different showing a higher proportion of males in the PD group (67.0% vs 46.2% in HC group, $p = 0.022$). PD patients were only mildly to moderately affected since all scored between stages 1 and 3 on the Hoehn & Yahr scale and between 1 and 3 on the CGI. Thirteen patients were not yet medicated at the time of evaluation. Ten patients were treated with L-Dopa in monotherapy, nine patients with dopaminergic agonists in monotherapy, and 77 with a combination of antiparkinsonian drugs.

All neuropsychological mean scores were within normal range. Patients and HC did not differ in terms of their Mattis DRS and FAB scores, the MoCA score (27.5±2.0 vs 28.3±1.3 in HC group, p = 0.028) was slightly lower in patients. PD patients also showed lower mood (HADS Depression: 3.8±2.9 vs 2.3±3.4, p = 0.008) and increased apathy (Starkstein: 9.5±5.0 vs 7.0 ± 3.6, p = 0.005) compared to the HC.

[insert Table 1]

Comparison of social cognitive profile between PD patients and Healthy Controls

PD patients obtained significantly lower scores than HC on the global SC score (p = 0.013), as well as the emotional identification task (p = 0.022) and the ToM task (p = 0.017). The strength of impairment was similar between the three SC scores (global f2 = 0.06, emotional task f2 = 0.04, ToM f2 = 0.05). In the emotional identification task, only negative emotions were not well identified by the patients, mainly fear and sadness. None of the six questions composing the Faux-Pas score were significantly different between patients and HC after multiple corrections, although a tendency was observed for detection, understanding and intentionality. Raw scores are shown in Table 1 and Table S2.

Factors influencing social cognition in PD

We found no global effect of age, gender, education level, severity of disease (MDS-UPDRS III Off), dopaminergic treatment (LEDD, dopaminergic agonist EDD), mood (HADS depression), anxiety (HADS anxiety), apathy (Starkstein scale) and ICD (ASBPD) on global Mini-SEA, as well as emotional and ToM tasks scores. Only the FAB had an influence on the global Mini-SEA score (f2 = 0.24, p<0.001), as well as on the two subtests. The effect was

more pronounced for the ToM task ($f2 = 0.19$, $p<0.001$) than for the emotional task ($f2 = 0.12$, $p = 0.001$).

Neuropsychological Profile Classification

The distribution of the four sub-groups (noMCI/noSCI, MCI/noSCI, noMCI/SCI, MCI/SCI) was different between PD patients and HC ($p=0.009$). MCI was observed in 15,6% of the PD patients (17 out of 109) and in only 2,6% of the controls (1 out of 39). In the PD group, we found that 30.3% (33 out of 109) of PD patients were impaired on their socio-emotional abilities. Moreover, 20.2% (22 out of 109) presented a selective socio-emotional deficit with preserved cognitive functions. Comparatively, no HC showed both cognitive and socio-emotional impairment and only 5% (2 out of 39) had impaired socio-emotional abilities (Figure 1).

[insert Figure 1]

Discussion

In our cohort, we found that a deficit in social cognitive abilities is frequent within the first four years of evolution after diagnosis. 30% of the patients were impaired on the socio-emotional abilities. Moreover, two-thirds of these patients was selectively impaired on SC with other cognitive functions being preserved. Furthermore, it appeared that social cognitive impairment (SCI) in isolation (20.2%) was 3.5 times more frequent than MCI in isolation (5.5%). Therefore, SCI represents the most common neuropsychological deficit in a population of PD patients at the early stages of the disease.

Our data showed that MCI and SCI can appear separately. Patients could present MCI only (MoCA < 26) or SCI only (Mini-SEA < 23.1). The independence of social cognition deficit from other cognitive impairments was recently reported[27]. Esteves al (2018)[27] found that 38.5% of patients with early PD showed impairment on social cognitive tests only and

not on executive tests, whereas 12.8% showed impairment on executive tests only and not on social cognitive tests in a smaller group of patients (N=39).

In our group of patients, both component of social cognition, emotional processes and Theory of Mind abilities, were affected. PD patients failed to identify negative emotions in the emotional task, mainly fear and sadness, whereas happiness was correctly identified, in line with results of previous studies[16]. In the "Faux Pas" Recognition test, patients performed almost as well as controls to attribute the blunder in the stories to the right person. However, a qualitative analysis detected more difficulties to infer the reason why the remark or act was inappropriate. PD patients showed a tendency to over interpret or to attribute wrong intentionality, as illustrated by Julie's story (where Julie's friend told her that the curtains in her new apartment are ugly and she should buy some new ones, while Julie had just bought them): several patients explained that Julie's friend made this unpleasant remark for retaliatory purposes or because the friend was angry with her. In addition, patients had also difficulties inferring the feelings experienced by the protagonist by proposing poor explanation, blunted and even erroneous emotion.

In accordance with prior findings, neither motor severity[9,12–14] nor dopamine replacement therapy[7,9,19,20] ad influence on SC abilities . We found an influence of the FAB performance on all the Mini-SEA scores. This finding is not surprising as several cognitive processes involved in SC are part of the executive functions, in particular working memory and inhibition control[9,16,17,18,20,21]. No influence of level of depression, anxiety, apathy and ICD was found, neither on emotion identification, nor on ToM abilities. To date, several studies reported no relation between depression level and SC abilities[13,19], but little attention has been paid to the impact of anxiety, apathy or ICD[20,28]. We did not find gender difference on emotional identification and on the ToM. Few studies investigated the influence of the gender

on emotional processes or ToM in PD and only one study showed more deficits in identifying fearful expressions in men[29].

The strengths of our study rely on its large number of patients and the investigation of different domains of social cognitive abilities. They are limitations. Our neuropsychological battery did not allow to distinguish between the different types of MCI[3]. We did not refer to the concept of Mild Behavioral Impairment (MBI)[30] that encompassed apathy, mood disorders, impulse dyscontrol, and psychotic symptoms and social cognitive impairment as very few patients presented apathy, impulse control disorders or hallucinations, beside social cognition impairment. We did not explore all dimensions of social cognition and we focussed on two aspects explored by the Mini-SEA: emotion identification and ToM. This strategy does not allow to draw general conclusions on the whole spectrum of social cognition alterations that may be found in PD.

Our study has two significant implications. From a clinical point of view, social cognitive impairment should be considered a major non-motor feature of PD that is independent from age, gender, level of education, depression, anxiety, motor deficit, dopaminergic agents, and with or without associated MCI. As a crucial prerequisite for social human interactions, social cognitive abilities are a determinant key in the quality of life of PD patients. Its impairment may therefore lead to conflicts in marital, familial, or professional interactions, often reported in PD patients[3] and contribute to isolation. This support the importance of offering adapted psychotherapy to the patient and his caregiver from the early stages of the disease.

We highlighted the presence of a sub-group of PD patients with isolated SCI and the absence of MCI, which is larger than the sub-group of PD patients with isolated MCI. From a conceptual point of view, we propose to single out this isolated SCI as "*Mild Social Cognitive Impairment*" (MSCI). This "Mild Social Cognitive Impairment" could be conceptualized as a

domain of MCI. Thus, we suggest expanding the phenomenology of MCI with the concept of MSCI as the sixth subtype of MCI.

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Graziella Mangone: 1) Research Project: B, C; 3) Manuscript: B

Jean-Christophe Corvol: 1) Research Project: A, B; 2.C; 3) Manuscript: B

Marie Vidailhet: 1) Research Project: A, B; 3) Manuscript: B

Richard Levy: 1) Research Project: A, B; 3) Manuscript: B