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Executive functioning and risk-taking behavior in Parkinson's disease patients with impulse control disorders

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ABSTRACT

Background: Impulse control disorders (ICD) are common in Parkinson's disease (PD) and are associated with dopaminergic medication. The purpose of this study was to investigate executive function and risk-taking behavior in PD patients with ICD.

Methods: 17 PD patients with ICD (ICD-PD) were compared to 20 PD patients without ICD (CTRL-PD) using neuropsychological and experimental tasks. Executive functions were assessed using standard executive testing (Conner's Performance Test, Modified Wisconsin Card Sorting Test, Trail Making Test and phonological verbal fluency). Subjects were also submitted to an experimental gambling task consisted of three decks of money cards: neutral deck (equal opportunity for gains as losses), winning deck (small amount of money with a positive balance) and loser deck (high amount of money with a negative balance), evaluating risk-taking behavior (number of cards picked in each deck) and valuation of the reward (subjective appreciation of the value of each deck).

Results: There was no significant difference in executive functioning between groups. Both groups selected more cards in the losing deck (high amount of money) as compared to the neutral deck (Mann-Whitney test, ICD-PD, p=0,02; CTRL-PD, p=0,003) and to the winning deck (Mann-Whitney test, ICD-PD p=0,0001; CTRL-PD p=0,003), suggesting an increased risk-taking behavior. Interestingly, we found that ICD-PD patients estimated the value of decks differently from CTRL-PD patients, taking into account mainly the positive reinforced value of the decks (Mann Whitney test, p=0,04).

Discussion: This study showed that executive pattern and risk-taking behavior are similar between ICD-PD and CTRL-PD patients. However, ICD-PD patients showed a specific deficit of the subjective estimation of the reward. Links between this deficit and metacognitive skills are discussed.

INTRODUCTION

Impulse control disorders (ICD) are behavioral disorders characterized by the failure to resist an impulse, inability to cut down and unsuccessful attempts to control a specific behavior (Evans et al. 2009). In Parkinson's disease (PD), the lifetime prevalence of ICD is about 14% (Weintraub et al. 2010). The most frequent ICD in PD are pathological gambling (PG), hypersexuality (HS), compulsive shopping (CS) and compulsive eating (CE) (Evans et al. 2009; Weintraub et al. 2010). The high prevalence of ICD in PD has been associated to the dopaminergic treatment, particularly to dopamine agonists (DA) (Weintraub et al. 2010). A possible hypothesis for the association between DA treatment and ICD involves their relative selectivity of D2-D3 dopamine-receptor. Those receptors are particularly abundant in the ventral striatum known to play a role in behavioral addiction and substance use disorders (Gurevich et al. 1999). In addition to DA exposure, clinical risk factors associated with ICD in PD are male gender, younger age, younger age at onset of PD and longer disease duration, personal or family history of alcohol or psychiatric disorders, high novelty seeking personalities, impulsivity and alexithymia traits (Weintraub et al. 2010; Voon et al. 2011a; Goerlich-Dobre et al. 2014). Although the pathological mechanisms remain largely unknown, the level of dopamine denervation of the fronto-striatal circuitry, involved in executive as well as decision-making functions, has been associated to ICD in PD (Cilia et al. 2011; Vriend et al. 2014). Especially, Cilia et al. (2011) found decreased prefrontal cortex, cingulate, insula, parahippocampal gyrus and striatal resting perfusion with increasing gambling severity in PG patients. These regions are involved in reward and risk processing, error detection, learning, decision-making and impulse control. Furthermore, the authors showed an anterior cingulate cortex-striatum disconnection, which could underline a specific impairment in ability to shift behavior after negative outcomes, leading patients to continue their behavior despite dramatic consequences.

A growing amount of studies attempted to investigate the cognitive characteristics associated with ICD in PD. Some studies found preserved cognitive functions (Siri et al. 2010; Djamshidian et al. 2011a; Mack et al. 2013). By contrast, a significant association between executive dysfunction and ICD has been demonstrated in few studies (Djamshidian et al. 2010; Vitale et al. 2011; Poletti et al. 2012). Especially, PD patients with PG had more severe impairments in retrieval of verbal and visuo-spatial information and cognitive flexibility (Santangelo et al. 2009). However, there were several limitations in these studies including materials used to explore cognitive functioning, often limited to working memory or global executive assessment.

Decision-making, connoting the process of choosing under ambiguous or risky situations the optimal selection in terms of rewarding or punishing outcomes between several alternative course

of actions (Paulus 2005), has been well documented in PD patients (Delazer et al. 2009) and has been specifically involved in PD patients with ICD (Djamshidian et al. 2010; Rao et al. 2010; Rossi et al. 2010; Steeves et al. 2009). Especially, Rossi et al. (2010) found that PD patients with PG obtained poorer performances in a risk-taking under ambiguity task that PD without PG. Using delay-discounting tasks, several studies showed that altered impulsivity in PD with ICD can contribute to risk-taking (Voon et al. 2010a; Housden et al. 2010). The physiopathology underlying risk-taking behavior in PD with ICD has been explored and involved dysfunction in the reward system including ventral striatum (Rao et al. 2010; Steeves et al. 2009). For example, using functional magnetic resonance imaging to quantify resting cerebral blood flow (CBF) and blood oxygenation level dependent (BOLD), Rao et al. (2010) showed that compared with non-ICD PD patients, PD patients with ICD demonstrated significantly reduced resting CBF in the right ventral striatum and significantly diminished BOLD activity in the right striatum during risk-taking. The influence of pharmacological status on risk taking and impulsivity in PD with ICD has also been explored (Voon et al. 2010b; Housden et al. 2010; Djamshidian et al. 2011a; Leroi et al. 2013). These studies broadly concluded that PD patients with ICD tend to make more impulsive and risky choices while ON dopamine agonist relative to those OFF dopamine agonists or without ICD**.**

Self-awareness, metacognitive skills and their links to ICD have also been recently explored (Brevers et al. 2013; Mack et al. 2013; Brevers et al. 2014). Self-awareness is usually evaluated by questionnaire as the Beck Cognitive Insight Scale (BCIS), assessing the understanding of patients' perspective about their anomalous experiences, their attribution and their aberrant interpretation of specific life events. Impaired self-awareness or insight has been recognized as a feature of a large number of neuropsychiatric disorders, including PD (Gilleen et al. 2010). Using the BCIS, Mack et al. (2013) compared self-awareness of cognitive and behavioral issue in PD patients with and without ICD and showed that PD patients with ICD are aware of their PD-related problems including impulsivity. In a different perspective, Brevers et al. (2013; 2014) studied how metacognitive sensitivity may influence gamblers without PD's decision-making. Metacognition was assessed by asking participants to wager on their own decision. They found that gamblers tend to wager high while performing poorly on the Iowa Gambling Task and in a non gambling task, suggesting that pathological gamblers exhibit impaired metacognition in both gambling like and more 'neutral' situations of decision-making**.**

The aim of the present study was to investigate executive functions with classical tasks and risk-taking behavior using a task developed to assess behavioral response and valuation of the reward in PD patients with ICD (ICD-PD) compared to PD controls patients without ICD (CTRL-PD).

PATIENTS AND METHODS

Subjects

Patients were selected from among those attending the movement disorders unit of the Pitié-Salpêtrière Hospital (Paris, France). All patients met the following inclusion criteria: idiopathic PD according to the United Kingdom Parkinson's Disease Society Brain Bank and absence of dementia, according to the MDS task-force criteria (Dubois et al. 2007). All patients obtained score higher than 130 on the MDRS. Exclusion criteria were a history of ICD prior to PD-onset and treatment by deep brain stimulation (DBS) before the ICD onset. Between January 2007 and January 2008, all patients suspected to have ICD in the interview with the neurologist received a specific evaluation of their ICD by a neuropsychologist. Presence and severity of active ICD were assessed with a semi-structured interview assessing behavior and mood in PD, the 'Ardouin Scale of Behavior in Parkinson's Disease' (ASBPD) (Ardouin et al. 2009; Rieu et al. 2015). Inclusion criteria for ICD-PD patients was a score ≥ 2 (moderate to severe) in at least one item in the ASBPD scale of pathological gambling, compulsive eating, compulsive shopping and hypersexuality. The ASBPD scale also evaluates compulsive DA and others hyperdopaminergic symptoms such as punding or any form of hobbyism. Patients who presented punding or form of hobbyism without ICD were not included in the study. CTRL-PD group was constituted of PD patients, matched with ICD-PD patients for age, sex, educational level, disease's severity and duration, and who were candidate for Deep Brain Stimulation (DBS) between the same period, without history of ICD. The CTRL-PD patients were, therefore, at risks for ICD; their absence was confirmed by a score ≤ 1 (none or mild) in all ICD's items of the ASBPD scale, described below. Informed consent was obtained from all individual participants included in the study.

Procedure

The two groups of patients underwent a comprehensive assessment of clinical, neuropsychiatric and neuropsychological functioning. Assessment was performed in a single session that lasted approximately 3 hours and when patients were in the 'on' state. Breaks were introduced to avoid fatigue.

Neurological assessment

Patients underwent a neurological examination consisting of the motor section of the Unified Parkinson's disease Rating Scale (UPDRS, section III) to measure the severity of motor symptoms in the 'on' state. Most of patients in both groups were at the motor fluctuations stage of the disease. The demographic data (age, educational level), neurological details (age at PD onset and PD duration) and treatments (medication type, total L-dopa equivalent daily dose (LEDD) and

total L-dopa equivalent daily dose (LEDD) of dopamine agonists) of each patient enrolled were recorded.

Psychological assessment

All patients underwent a psychological assessment consisting of the following:

1. the Montgomery and Asberg Depression Scale (MADRS) to evaluate depression, using only the dysphoria factor defined by Suzuki et al. 2005, naming items of reported sadness, pessimistic thoughts and suicidal thoughts to avoid confounding symptoms related to PD as 'lassitude', 'inability to feel' or 'concentration difficulties;
2. the Starkstein scale (Starkstein et al. 1992) to identify apathy state and the severity of apathetic symptom;
3. the Barrat Impulsiveness Scale (BIS-11) (Fossati et al. 2001), a global self-report scale of impulsivity;
4. the 'Ardouin Scale of Behavior in Parkinson's Disease' (ASBPD) (Ardouin et al. 2009; Rieu et al. 2015). The ASBPD consist of 21 items, grouped into four parts: general psychological evaluation (part I), apathy (part II), non-motor fluctuations (part III) and hyperdopaminergic behavior (part IV). Part I successively evaluates depressive mood, hypomanic mood, anxiety, irritability and aggressiveness, hyperemotionality, and psychotic symptoms. Part II evaluates apathy in behavioral terms, that is, activity level, cognitive level, and emotional level. Part III evaluates the psychological state associated with the motor symptoms in the OFF and ON states in fluctuating patients. Part IV assesses the presence and the intensity of behavioral disorders induced by dopaminergic treatment, including nocturnal hyperactivity, diurnal somnolence, eating behavior, creativity, hobbyism, punding, risk-taking behavior, compulsive shopping, pathological gambling, hypersexuality, dopaminergic addiction, and excess in motivation. The timeframe of the assessment is the preceding month. Each item is rated on a five-point scale (severe disorder, 4; marked disorder, 3; moderate disorder, 2; mild disorder, 1; absence of disorder, 0), by taking into account the severity and the frequency of the disorder and its impact. The interview is completed by a psychiatrist, a neuropsychologist, or a clinical psychologist familiar with PD and neuropsychiatric disorders in movement disorders. Total completion time is approximately 1 hour.

Neuropsychological assessment

All PD patients underwent neuropsychological tasks to assess executive functioning and risk-taking behavior. The Conner's Performance Test (CPT-II) (Connors 2004), a 15 minutes computerized test, was used to evaluate attention and inhibition. The subject had to press the space bar of the computer as soon as he sees any letter on the screen, except the letter X, that he has to

hold back and press nothing. Variability in reaction time (expressed in millisecond) was used to assess attention capacity. Percentage of commission error (press when the letter is X) referred to inhibition abilities. The executive functioning was also assessed using : 1) conceptualization capacities measured by the reached number of criterion (range from 0 to 6) in the Modified Wisconsin Card Sorting Test (MCST) (Milner 1963); 2) shifting and reactive flexibility evaluated by the difference between the time scores of TMT-B and TMT-A in the Trail Making Test (TMT) (Reitan et al. 1985); 3) spontaneous flexibility and cognitive auto-activation skills using the phonological verbal fluency R with the total number of correct words given in 2 minutes (Cardebat et al. 1990).

To assess risk-taking behavior, we used a gambling task adapted from the Iowa Gambling Task (IGT) (Bechara et al. 1994). The subject saw on a screen 3 decks of cards labeled A, B, and C. Every time the subject picked a card, a message was displayed on the screen indicating the amount of money he immediately won or lost. At the same time, on the top of the screen, the total amount of money was displayed. The subject was asked to choose 50 cards and to win as much money as possible. Contrary to the IGT, subject was notified that some decks were more advantageous than others in order to avoid ambiguity and facilitate the comprehension of the rule. At the end of the task, subject was asked to appreciate if each deck was a winning, a losing or a neutral deck (called subjective variables). Subject can evaluate several decks as winning, losing or neutral. Decks had been constructed so that deck A was a neutral deck (equal opportunity for gains as losses). Deck B (small amount of money with a positive balance) was the winning deck with small gains but smaller losses. Deck C can be considered as the losing deck (high amount of money with a negative balance) as the subject won big gains but lost even more. Objective variables were the number of cards chosen in each deck. The score for each objective variable ranges from 0 to 50. The score for each subjective variable (valuation of the reward by appreciation of each deck) ranged from 0 to 2 (0: loser deck; 1: neutral deck; 2: winner deck). This adaptation of the IGT was proposed to avoid ambiguity and to focus on the ability to resist to a big risky reward for the benefit of a smaller but safer reward rather than the capacity to detect and understand the rule. Especially, risk-taking behavior is evaluated by comparing the number of cards picked in each deck, subjects being aware of the advantageous/disadvantageous characteristic of the decks and constantly informed of his immediate reward and the total amount of money. Moreover, due to subjective variables, this task takes into account the valuation of the reward.

Statistical Analysis

For demographic characteristics and neuropsychological data a Mann-Whitney U-test or a Fisher exact test were used to compare CTRL-PD and ICD-PD groups. For risk-taking task,

comparison between the 3 groups (HV, CTRL-PD, ICD-PD) and between the three decks (A, B, and C) were performed by using a Kruskall Wallis test, followed when significant by a comparison of each group by a Mann-Whitney U-test. All results were considered significant if the p-value was less than 0.05 with no correction for multiple comparisons. Data were expressed as median +/- upper and lower quartiles. Statistical analysis was performed using Statistica 9.1 software (StatSoft France, F-94700, Maisons-Alfort).

RESULTS

Patients' characteristics

Thirty-seven patients (age range 33-69 years, men/women = 27/10) participated in this study. Seventeen patients were diagnosed as having one or more active ICD as the time of assessment. In ICD-PD group, specific criteria of the ASBPD confirmed presence of PG in 6 patients, HS in 1 patient, CS in 2 patients, CE in 2 patients and 6 patients had multiple ICD (i.e. hypersexuality and pathological gambling or compulsive shopping and pathological gambling). Twenty patients without history of ICD were included in the CTRL-PD group (score ≤ 1 in all ICD's items of the ASBPD scale).

The two groups did not differ in gender, age, educational level, age at PD onset, PD duration, LEDD dopamine agonist dose, UPDRS-III while "on" state and MDRS score (see results in table 1). However, the 2 groups differed in total LEDD (p =0,003), possibly because CTL-PD patients were recruited among those candidate for DBS and therefore needed more dopaminergic treatment to control the disease.

For neuropsychiatric characteristics, the two groups differed in MADRS dysphoria score (p = 0,01), in Starkstein score (p = 0,01) and in the BIS-11 score (p = 0,003).

[Insert Table 1]

Executive functions

The two groups did not differ in attention capacities, conceptualization abilities, reactive flexibility, spontaneous flexibility and inhibition capacities.

[Insert Table 2]

Risk-taking behavior results

For the risk-taking task, the two groups of PD patients were compared to fifteen healthy volunteers (HV) matched in age, sex and educational level on the objective variables (number of

cards chosen in each deck) and the subjective variables (appreciation of each deck: winning, neutral or losing deck).

For each selection, all patients were able to clearly identify the feedback they received.

First, we analyzed the pattern of performances inside each group. For HV, there was no significant difference between decks for both objective and subjective variables (Kruskall-Wallis test, $p = 0.61$ and $p = 0.13$ respectively). On the contrary, ICD-PD patients and CTRL-PD patients both showed significant differences of the number of cards in each deck (Kruskall Wallis, $p = 0.004$ for CTRL-PD, $p = 0.007$ for ICD-PD). For both groups, the number of cards chosen in the losing deck C (high amount of money) was higher as compared to the neutral deck A (Mann-Whitney test, ICD-PD, p=0,02 ; CTRL-PD, p=0,003) and to the winning deck B (small amount of money) (Mann-Whitney test, ICD-PD p=0,0001 ; CTRL-PD p=0,003). In addition, in the ICD-PD group, the number of card chosen in winning deck B was significantly lower than in neutral deck A (Mann-Whitney test, $p = 0.04$). Subjective variables were not significantly different in the HV or the CTRL-PD groups (Kruskall-Wallis test, $p = 0.13$ and $p = 0.45$ respectively) whereas they were significantly different in the ICD-PD group (Kruskall-Wallis test, $p = 0.01$). ICD-PD patients evaluated the wining deck B (small amount of money) loser as compared to neutral deck A (Mann-Whitney, $p = 0.04$) and losing deck C (Mann-Whitney, p=0,01).

Then, we compared the performances between the three different groups. When comparing PD patients to HV, we found no significant difference between HV and CTRL-PD groups for both objective and subjective variables. Furthermore, the ICD-PD group was significantly different from the HV for both variables: ICD-PD patients chose significantly less frequently the winning deck B (Mann Whitney, p=0,04) and evaluated this deck more frequently as a losing one (Mann Whitney, p=0,02) as compared to HV. Moreover, ICD-PD patients evaluated the losing deck C more frequently as a winner than HV (Mann Whitney, p=0,02). ICD-PD patients and CTRL-PD patients did not significantly differ for any deck for objective variables. Furthermore, for subjective variables, ICD-PD patients evaluated the winning deck B more frequently as a loser one than the CTRL-PD patients (Mann Whitney test, p=0,04).

[Insert Table 3]

DISCUSSION

This study examined executive functioning and risk-taking in PD patients with ICD. As previously observed by Weintraub et al. (2010) and Voon et al. (2011a), we found that ICD-PD patients showed greater impulsivity, more depressive elements and lack of motivation than PD-CTRL patients.

Concerning the executive functioning, we found that ICD-PD patients performed similarly than CTL-PD patients, as supported by other studies, which showed no executive dysfunction including set shifting, inhibitory process and reactive flexibility in ICD patients compared to CTRL PD patients (Siri et al. 2010; Djamshidian et al. 2011a; Mack et al. 2013). This is against previous reports showing a positive association between ICD and cognitive dysfunction (Santangelo et al. 2009; Vitale et al. 2011). Methodological and PD population's differences as well as small size of groups can highlight those discrepancies.

In this study, we addressed to the patients an experimental task to investigate risk-taking behavior and valuation of the reward. Our results showed that contrary to HV, both groups of PD patients behave similarly, choosing more frequently cards in the loser deck (high amount of money) compared to the other decks. These results confirm risk-taking behavior in PD with or without ICD (Delazer et al. 2009; Djamshidian et al. 2010; Rossi et al. 2010). Risk-taking behavior in PD probably involved dopamine replacement therapy's influence on mesolimbic spared circuit. For example, Steeves et al. (2009) in a PET neuroimaging study in PD patients with PG demonstrated decreased ventral striatal D2/D3 binding potential at baseline and a relatively greater decrease in binding potential in the ventral striatum during performance of a gambling task. Consistent with our results, Rao et al. (2010) found that both ICD-PD and CTL-PD groups behave similarly in a risk-taking task. Interestingly, in that functional magnetic resonance imaging, the authors showed that contrary to CTL-PD patients, ICD-PD patients demonstrated relatively diminished activity in the ventral striatum during risk-taking.

Our results suggested also that ICD-PD patients showed a specific deficit of the subjective estimation of the reward compared to patients without ICD, taking into account mainly the positive reinforced value of the decks, and less considering the value of the loss. These results are in line with studies exploring reinforcement sensitivity, demonstrating that via action on ventral striatal dopamine function, dopamine replacement therapy could potentially alter reward responsiveness and abilities to learn from negative decision outcomes (Franck et al. 2004; Pessiglione et al. 2006; Piray et al. 2014). For example, Franck et al. (2004) showed that PD patients without ICD have different learning and reward-seeking behaviors from healthy controls. PD patients showed exactly opposite learning patterns during their medication ON and OFF states: PD patients achieved more efficient learning by positive reinforcement during their ON medication state, whereas they performed better through negative feedback during their medication OFF state. In ICD-PD patients, it seems that dopamine agonist enhance the deviated learning pattern. Voon et al. (2010b) showed that dopamine agonist enhance the rate of a gain-specific learning and increase striatal prediction error activity observed in patient with ICD. Thus, ICD-PD patients can experiment a persistent "better than expected" outcome while taking dopamine agonist. Dopamine agonists also enhance

risk-taking behavior in ICD-PD patients (Voon et al. 2011b). While taking dopamine agonists, these patients seem to have a bias towards risky choice independent of the effect of loss aversion. Especially, Voon et al. (2011b) showed that neural activity in brain areas associated with risk representation, such as the ventral striatum, orbitofrontal cortex and anterior cingulate cortex, are decreased in these patients.

In our study, both PD groups presented risk-taking behavior during the task but only ICD-PD patients presented deficit in subjective appreciation of the reward. Especially, despite risk-taking behavior, when they were asked about their perception of deck's value at the end of the task, CTL-PD patients were able to correctly appreciate the reward. In contrary, ICD-PD patients presented a specific deficit of the subjective estimation of the value of stimuli. Recent studies focusing on influence of metacognitive skills on risk-taking process can probably contribute to understand this specific deficit presented by our ICD-PD patients. Metacognition is the ability to cognizant and have insight about the quality of the decision and to accurately judge whether the decision is surely a good one or not. Brevers et al. (2013) studied how metacognitive sensitivity may influence gamblers without PD's decision-making during the Iowa Gambling Task. Metacognition was assessed by asking participants to wager on their own decision. They found that gamblers tend to wager high while performing poorly on the Iowa Gambling Task and that the difference was not due to reward/loss sensitivity, current clinical or cognitive status. The same authors in a more recent study (Brevers et al. 2014) replicated these results with a non gambling task (grammatical paradigm). They found that compared to healthy volunteers, pathological gamblers without PD also erroneously think that they are performing much better than they actually are. Both studies suggested that pathological gamblers exhibit impaired metacognition in both gambling like and more 'neutral' situations of decision-making. In our study, the erroneous appreciation of deck’s values specifically presented by ICD-PD patients could be linked to deficit in metacognitive skills. Indeed, in these patients, introspection’s abilities are possibly based on the under-optimal behavior and lead to focus on the positive reinforcement value. In that perspective, Djamishidian et al. (2011b) showed that PD patients with ICD learn little of their mistakes, compared to ICD patients without PD. On the contrary, a recent study evaluating self-awareness in PD patients with ICD showed that presence of ICD was associated with awareness of impulsive behaviors, as indexed by greater cognitive insight into thoughts and behaviors on the BCIS (Mack et al. 2013). In the different studies cited above, different levels of awareness are probably involved and might explain the discrepancies of the results. All together, these results showed that ICD-PD patients are probably aware of ICD, but exhibit a fundamental impairment in their perception of winning or losing behaviors among various situation of decision-making and provide an interesting perspective to explain how metacognitive skills can contribute to the deficit of subjective estimation of the

reward presented by our ICD-PD patients.

There are however some limitations to our study. First, our sample size was small and may not have provided adequate power to detect smaller differences across variables. Second, this study focused on risk-taking behavior using an adapted task of the IGT to avoid fatigue, involvement of working memory and ambiguity in order to focus on the ability to resist a big risky reward for the benefit of a smaller but safer reward. This adaptation provides interesting results concerning risk-taking behavior in line with other studies (Rossi et al. 2010; Rao et al. 2010). Nevertheless, this experimental task is limited to the optimal selection in terms of rewarding or punishing outcomes under risky situations. The absence of ambiguity in our task reduces the interpretation in terms of decision-making process. Finally, a valuation of the reward was explored by an indirect measure (appreciation of each deck at the end of the risk-taking task) limiting the interpretation in terms of reward sensitivity. Despite these limitations, our study provides interesting findings on subjective perception of the reward, showing that subjective valuation of the reward is specifically impaired in PD patients with ICD compared to CTL-PD patients.

In summary, our results show that executive pattern and risk-taking behavior are similar between ICD-PD patients and CTRL-PD patients, but patients with ICD present a specific deficit of the subjective estimation of the reward compared to CTRL-PD patients. Studies focusing on metacognitive skills provide an interesting perspective to explain our results. In that perspective, introspection's abilities of ICD-PD patients, possibly based on the under-optimal behavior, lead ICD-PD patients to focus on the positive reinforcement value. Others studies exploring subjective estimation of the reward and metacognitive skills are necessary to better understand their link and their influence on risk-taking behavior in PD patient with ICD.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

REFERENCES

Ardouin C, Chéreau I, Llorca PM, et al (2009) [Assessment of hyper- and hypodopaminergic behaviors in Parkinson's disease]. Rev Neurol 165:845-856. doi: 10,1016/j.neurol.2009.06.003

Bechara A, Damasio AR, Damasio H, Anderson SW (1994) Insensitivity to future consequences following damages to human prefrontal cortex. Cognition 50:7-15.

Brevers D, Cleeremans A, Bechara A, et al (2013) Impaired self-awareness in pathological gamblers. J Gamb 29:119-129. doi: 10.1007/s10899-012-9292-2

Brevers D, Cleermans A, Bechara A, et al (2014) Impaired metacognitive capacities in individual with problem gambling. J Gamb Stud 30:141-152. doi: 10.1007/s10899-012-9348-3.

Cardebat D, Doyon B, Puel M, Goulet P, Joannette Y. (1990) Formal and semantic lexical evocation in normal subjects. Performance and dynamics of production as a function of sex, age and educational level. Acta Neurol Belg 90:207-217.

Cilia R, Cho SS, Van Eimeren T, et al (2011) Pathological gambling in patients with Parkinson’s disease is associated with fronto-striatal disconnection: a path modeling analysis. Mov Disord 26:225-233. doi: 10.1002/mds.23480.

Connors K. Conners’s Continous Performance Test II (CPT-II V.5). 2004 Toronto: Multi-Heath Systems Inc.

Delazer M, Sinz H, Zamarian L, et al (2009) Decision-making under risk and under ambiguity in Parkinson's disease. Neuropsychologia 47:1901-1908. doi: 10.1016/j.neuropsychologia.2009.02.034.

Djamshidian A, Jha A, O'Sullivan SS, et al (2010) Risk and learning in impulsive and nonimpulsive patients with Parkinson's disease. Mov Disord 25:2003-2010. doi: 10.1002/mds.23247.

Djamshidian A, O'Sullivan SS, Lees A, Averbeck BB (2011a) Stroop test performance in impulsive and non impulsive patients with Parkinson's disease. Parkinsonism Relat Disord 17:212-

214. doi: 10.1016/j.parkreldis.2010.12.014.

Djamshidian A, O'Sullivan SS, Wittmann BC, Lees AJ, Averbeck BB (2011b) Novelty seeking behavior in Parkinson's disease. Neuropsychologia 49:2483-2488. doi: 10.1016/j.neuropsychologia.2011.04.026.

Dubois B, Burn D, Goetz C et al (2007) Diagnostic procedures for Parkinson's disease dementia: recommendations from the movement disorder society task force. Mov Disord. 22:2314-2324.

Evans AH, Strafella AP, Weintraub D, Stacy M (2009) Impulsive and compulsive behaviors in PD. Mov Disord 24:1561-1570. doi: 10.1002/mds.22505.

Fossati A, Di Ceglie A, Acquarini E, Barratt ES (2001) Psychometric properties of an Italian version of the Barrat Impulsiveness Scale-11 (BIS-11) in nonclinical subjects. J Clin Psychol 57:815-828.

Franck MJ, Seeberger LC, O'Reilly RC (2004) By carrot or by stick : cognitive reinforcement learning in parkinsonism. Science 306:1940-1943.

Gilleen J, Greenwood K, David A (2010) Lack of Insight and Awareness in Schizophrenia and Neuropsychiatric Disorders, in Neuropsychiatric Disorders, 1st Edition, Edited by Miyoshi K, Morimura Y, Maeda K. Springer Publising. 33-49

Goerlich-Dobre KS, Probst C, Winter L, et al (2014) Alexithymia-An independent risk factor for impulsive-compulsive disorders in Parkinson's disease. Mov Disord 29:214-220. doi: 10.1002/mds.25679

Gurevich EV, Joyce JN (1999) Distribution of dopamine D3 receptor expressing neurons in the human forebrain: comparison with D2 receptor expressing neurons. Neuropsychopharmacology 20:60-80.

Housden CR, O'Sullivan SS, Joyce EM, Lees AJ, Roiser J (2010) Intact reward learning but elevated delay discounting in Parkinson's disease patients with impulsive-compulsive spectrum behaviors. Neuropsychopharmacology 235:2155-2164. doi: 10.1038/npp.2010.84.

Leroy I, Barraclough M, McKie S, Hinvest N, Evans J, Elliott R, McDonald K (2013) Dopaminergic influences on executive function and impulsive behavior in impulse control disorders in Parkinson's disease. J Neuropsychol 7:306-325. doi: 10.1111/jnp.12026.

Mack J, Okai D, Brown RG, et al (2013) The role of self-awareness and cognitive dysfunction in Parkinson's disease with and without impulse-control disorder. J Neuropsychiatry Clin Neurosci 25:141-149. doi: 10.1176/appi.neuropsych.12030076.

Milner B (1963) Effects of different brain lesions on card sorting: the role of the frontal lobes. Arch Neurol 9:90-100.

Paulus MP (2005) Neurobiology of decision-making: quo vadis? Brain Res Cogn Brain Res 23:2-10.

Pessiglione M, Seymour B, Flandin G, Dolan RJ, Frith CD (2006) Dopamine-dependent prediction errors underpin reward-seeking behavior in humans. Nature 442:1042-1045.

Piray P, Zeighami Y, Barhami F, Eissa AM, Hewedi DH, Moustafa AA (2014) Impulse control disorders in Parkinson's disease are associated with dysfunction in stimulus valuation but not action valuation. J Neurosci 34:7814-7824. doi: 10.1523/JNEUROSCI.4063-13.2014.

Poletti M, Bonuccelli U (2012) Impulse control disorders in Parkinson's disease: the role of personality and cognitive status. J Neurol 259:2269-2277. doi: 10.1007/s00415-012-6506-6.

Rao H, Mamikonyan E, Detre JA, Siderowf AD, Stern MB, Potenza MN, Weintraub D (2010) Decreased ventral striatal activity with impulse contrl disorders in Parkinson's disease. Mov Disord 25:1660-1669. doi: 10.1002/mds.23147.

Reitan RM, Wolfson D. The Trail making Test. 1985 Tucson, A.Z: Neuropsychological Press.

Rieu I, Martinez-Martin P, Pereira B, et al (2015) International validation of a behavioral scale in Parkinson's disease without dementia. Mov Disord 30:705-713. doi: 10.1002/mds.26223.

Rossi M, Gerschcovich ER, De Achaval D, et al (2010) Decision making in Parkinson's disease patients with and without PG. Eur J Neurol 17:97-102. doi: 10.1111/j.1468-1331.2009.02792.x.

Santangelo G, Vitale C, Trojano L, Verde F, Grossi D, Barone P (2009) Cognitive dysfunctions and pathological gambling in patients with Parkinson's disease. Mov Disord 24:899-905. doi: 10.1002/mds.22472.

Siri C, Cilia R, De Gaspari D, et al (2010) Cognitive status of patients with Parkinson's disease and pathological gambling. J Neurol 257:247-252.doi: 10.1007/s00415-009-5301-5.

Starkstein SE, Mayberg HS, Leiguarda R, Preziosi TJ, Robinson R (1992). A prospective longitudinal study of depression, cognitive decline, and physical impairments in patients with Parkinson’s disease. J Neurol Neurosurg Psychiatry 55:377-382.

Steeves TD, Miyasaki J, Zurowski M, et al (2009) Increased striatal dopamine release in Parkinsonian patients with pathological gambling: a [11C] raclopride PET study. Brain 132:1376-1385. doi:10.1093/brain/awp054.

Suzuki A, Aoshima T, Fukasawa T, et al (2005) A three-factor of the MADRS in major depressive disorder. Depress Anxiety 21:95-97.

Vitale C, Santangelo G, Trojano L, et al (2011) Comparative neuropsychological profile of pathological gambling, hypersexuality and compulsive eating in Parkinson's disease. Mov Disord 26:830-836. doi: 10.1002/mds.23567.

Voon V, Reynolds B, Brezing C, et al (2010a) Impulse choice and response in dopamine agonist-related impulse control behaviors. Psychopharmacology 207:645-659. doi: 10.1007/s00213-009-1697-y.

Voon V, Pessiglione M, Brezing C, et al (2010b) Mechanisms underlying dopamine-mediated reward bias in compulsive behaviors. Neuron 65:135-142 doi: 10.1016/j.neuron.2009.12.027.

Voon V, Sohr M, Lang AE, et al (2011a) Impulse control disorders in Parkinson's disease: a multicenter case-control study. Ann Neurol 69:986-996. doi: 10.1002/ana.22356.

Voon V, Gao J, Brezing C et al (2011b) Dopamine agonists and risk: impulse control disorders in Parkinson's disease. Brain 134:1438-1446. doi: 10.1093/brain/awr080.

Vriend C, Nordbeck AH, Booij J, et al (2014) Reduced dopamine transporter binding predate

532 impulse control disorders in Parkinson's disease. Mov Disord 29:904-911. doi: 10.1002/mds.25886.
533 Weintraub D, Koester J, Potenza MN, et al (2010) Impulse control disorders in Parkinson's
534 disease: a cross-sectional study of 3090 patients. Arch Neurol 67:589-595. doi:
535 10.1001/archneurol.2010.65.

TABLES

Table 1: Demographic and clinical aspects of PD patients with and without ICD

Values are median (lower-upper quartile). P-value: Mann-Whitney test between groups.

Characteristics	ICD-PD n = 17	CTL-PD n = 20	p
Men/Women, No	14/3	13/7	0,24
Age (Yr)	55 (37-69)	55 (40-62)	0,52
Education (Yr)	7 (3-7)	7 (3-7)	0,45
Age at PD onset (Yr)	48 (32-65)	48 (35-55)	0,57
PD duration (Yr)	7 (2-10)	5,5 (4-12)	0,60
LEDD (mg/dose)	897,5 (299,88-1247,33)	1049,89 (527,05-1549,84)	0,003
LEDD dopamine agonist (mg/dose)	299,94 (77-718)	340,23 (66,68-700)	0,78
UPDRS-III score while on state	7 (0-23)	8,5 (0-34)	0,62
Dysphoria specific MADRS score	6 (0-13)	1,5 (0-7**)**	0,01
Starkstein scale score	7 (3-14)	4 (0-10)	0,01
MDRS score	140 (133-144)	139 (131-143)	0,07

Table 2: Neuropsychological compares between patients with PD with and without ICD.

Values are median (lower-upper quartile). P-value: Mann-Whitney test between groups.

	ICD-PD n = 17	CTL-PD n = 20	p
Impulsivity			
Global BIS-11	63 (48-81)	52 (36-70)	0,003
Attention			
RT variability CPT	88,5 (4,74-202,2)	82,9 (3,05-193,4)	0,68
Executive functioning			
criterion number MSCT	6 (5-6)	6 (3-6)	0,23
TMT B-A	34 (6-149)	45,2 (10-78)	0,56
fluency R	26 (6-43)	20 (8-38)	0,08
% commission CPT	22,2 (4,7-38,9)	20,8 (5,6-70,8)	0,67

Table3: Compares between the two PD groups and the healthy volunteers on the risk-taking task

Values are median (lower-upper quartile). P-value: Kruskal-Wallis test for each deck between groups.
[a]Significantly different from HV ; [b]Significantly different from CTL-PD ; [c]Significantly different from deck B ; [d]Significantly different from deck C, Mann Whitney test.

	ICD-PD n = 17	CTL-PD n = 20	HV n = 15	p
Objective variables				
Number of cards neutral deck A	17 (7-14) [d]	15 (8-23) [d]	15 (6-24)	0,58
Number of cards winning deck B	14 (5-18)[a, d]	15 (5-26) [d]	17 (10-33)	0,01
Number of cards losing deck C	19 (12-33)	20 (12-34)	16 (10-30)	0,21
Subjective variables				
Appreciation neutral deck A	2 (0-2) [c]	1 (0-2)	1 (0-2)	0,24
Appreciation winning deck B	0 (0-2) [a, b,d]	1,5 (0-2)	2 (0-2)	0,04
Appreciation losing deck C	2 (0-2) [a]	1,5 (0-2)	0 (0-2)	0,06