Reward sensitivity in Parkinson's patients with binge eating

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ABSTRACT

Background: Parkinson's disease (PD) patients who are treated with dopamine replacement therapy are at risk of developing impulse control disorders (ICDs) (such as gambling, binge eating, and others). According to recent evidence, compulsive reward seeking in ICDs may arise from an excessive attribution of incentive salience (or 'wanting') to rewards.
Objectives: In this study, we tested this hypothesis in patients with PD who developed binge eating (BE).
Methods: Patients with BE, patients without BE, and healthy controls performed different experimental tasks assessing food liking and wanting. Participants first rated the degree of liking and wanting for different foods using explicit self-report measures. They then performed an affective priming task that measured participants' affective reactions towards foods (liking), and a grip-force task that assessed their motivation for food rewards (wanting). All participants also completed several questionnaires assessing impulsivity, reward sensitivity, anxiety and depression, and underwent a neuropsychological evaluation.
Results: Patients with BE displayed an altered liking for sweet foods compared to controls but not to patients without BE. Furthermore, this difference emerged only when implicit measures were used. Importantly, an increased wanting was not associated with binge eating even if wanting, but not liking scores significantly correlated with LED levodopa, confirming the hypothesis of a distinction between the two components of rewards. Lastly, binge eating was associated with depression and lower working memory scores.
Conclusions: Take together these results suggest that binge eating in PD is associated with cognitive abnormalities, and to lesser extent affective abnormalities, but not with an increased incentive salience.

1. Introduction

Parkinson's disease (PD) patients who are treated with dopaminergic medications are at risk of developing impulse control disorders (ICDs), which include pathological and repetitive behaviors such as gambling, compulsive shopping, sexual behaviors, binge eating, compulsive use of dopaminergic medications and punding [1]. These disorders occur with percentages varying from 3.5% to 42.8% and they are believed to reflect the interaction of dopaminergic treatments (dopamine agonists and/or dopamine replacement therapy) with the individual's susceptibility and the underlying neurobiology of PD [2,3].

Several fMRI and PET studies support the hypothesis that ICDs, like addictive disorders, may be characterized by an excessive attribution of "incentive salience" (or 'wanting') to rewards. These studies have shown an increased activity in different reward brain regions after reward presentation in PD patients with ICDs compared to control patients [4–7], and that 'wanting' but not 'liking' ratings in these patients significantly correlate with the activity in the ventral striatum [5,7]. Even in behavioral tasks, ICDs patients have also shown to exhibit an increased willingness to work for a reward compared to patients without ICDs [5]. These findings are in line with the incentive sensitization theory, according to which the degree of 'wanting' for a reward increases disproportionately compared to the degree of which the reward is liked as patients develop an addictive disorder. Liking and wanting

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are indeed considered as separate reward components, mediating, respectively, the pleasure effect of a reward and the motivational drive toward it [8].

Among ICDs, binge eating (BE) is described as recurrent episodes of increased eating coupled with a perceived lack of control [9]. It occurs in 4.3% of PD patients taking dopaminergic medications, it is more common in women [10,11], and it is often associated with increased body weight [12]. In binge eater patients without PD, this disorder has been related to the mechanisms implicated in addictive disorders, including elevated motivation to seek out palatable foods, greater neural activation in reward-related circuitry to high-calorie foods, and impairment in cognitive control [13]. However, to date the hypothesis of an enhanced incentive salience attribution to reward in ICDs has never been tested in patients with BE.

To fill this gap, PD patients with BE, PD patients without BE and healthy controls performed several tasks assessing food liking and wanting. First, in order to measure the patients' conscious and subjective experience of food rewards, we had them rate the degree of "liking" and "wanting" for different foods using explicit self-reports. Second, participants performed an affective priming task that measures attitude and affective reactions towards foods, and a grip-force task, in which motivation towards rewards was indirectly operationalized as the exerted effort. Participants also underwent a series of neuropsychological tests and completed several questionnaires evaluating impulsivity, reward sensitivity and the presence of anxiety and depression.

2. Methods

2.1. Subjects

Thirty-one dopaminergic treated patients with PD and twenty healthy controls (C) took part in the study. PD patients were recruited from the movement disorders clinic of "Cattinara" hospital in Trieste (Italy). Patients were assessed by a neurologist and asked to fill the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS) [14]. Since no validation on the Italian population is available, we used a translated version of the questionnaire. Sixteen PD participants were identified as binge eaters (PD + BE), with ten exhibiting at least one additional ICDs (see supplementary material, Table S1). The other fifteen PD patients (PD) had no history of BE or other ICDs. Patients' disease severity was assessed using the Unified Parkinson's Disease Rating Scale-Part III (UPDRS-III) and the Hoehn and Yahr scale (H&Y) [15]. In addition, for each patient a daily L-dopa equivalent dose (LED total) was calculated based on [16]. The study was approved by SISSA Ethics Committee and all participants provided written informed consent. For details on demographical and clinical data, see Table 1.

Table 1
Demographic, clinic and questionnaire data (mean and standard deviation). Subscales of the questionnaires are provided in Italics.

	PD + BE (n = 16)	PD (n = 15)	C (n = 20)
Gender (female)	8	7	10
Age(y)	67.1(8.2)	64.9 (12.9)	68 (6.4)
Education (y)	9.6 (4.2)	10.7 (2.9)	9.7 (3.4)
BMI	29.4 (5.9)*,**	25 (3.8)	25.2 (3.4)
PD duration (y)	8.5 (5.6)	6.8 (3.1)	–
UPDRS III	20.5 (9.6)	15.8 (8.1)	–
H&Y	1.7 (0.4)	1.7 (0.4)	–
LED total (mg)	788 (260.7)	695.7 (309.3)	–
LED-DA (mg)	181.5 (51.7)	220.6 (83.9)	–
LED-Levodopa (mg)	476.5 (231.2)	348.3 (280)	–
Total QUIP-RS score	31.6(15.4)*	10.2 (10.2)	–
eating	8.9 (2.2)*	2 (1.8)	–
gambling	1.31 (2)	0.4 (0.9)	–
buying	4.7 (2.5)*	1.6 (1.4)	–
sex	2.7 (2.7)	1.8 (1.8)	–
hobbyism	5.8 (4.9)*	1.6 (2)	–
punding	3.5 (3.5)	1.3 (1.7)	–
DDS	3.8 (5.1)	1.4 (2.5)	–
HADS *anxiety* [a]	8.6 (4)	6.4 (3.8)	6.3 (3.5)
HADS *depression* [a]	7.6 (4.3)*,**	4.8 (2.3)	4.8 (3.2)
BIS impulsivity	60.1 (9.5)	57.4 (10.2)	63.1 (8.3)
attentional	15.6 (3.3)	14.5 (2.7)	16.3 (3.3)
motor	20.3 (3.5)	18.8 (4.5)	20.5 (3.5)
non-planning	25.1 (4.7)	28.8 (7.4)	26.3 (4.7)
BAS	38.5 (3.8)	39.2 (7.1)	40.2 (5.6)
reward responsiveness	17.5 (2.8)	16.6 (3.1)	17.6 (2.3)
drive	11.8 (1.8)	12.5 (3.9)	11.9 (2.3)
fun-seeking	9.1 (2.6)	10 (4.5)	10.6 (1.9)

* = significantly different from PD, $p < 0.05$;** = significantly different from C, $p < 0.05$;y = years;mg = milligrams;*a* = one patient didn't complete the HADS.

2.2. Experimental evaluation

We collected participant's subjective ratings of hunger and fasting in order to control for macroscopic differences between subjects. We collected participants' weight and height, and calculated body mass index (BMI) by dividing weight in kilograms by the square of height in meters (kg/m^2). Participants were then asked to perform the experimental tasks, undergo a neuropsychological examination and complete several questionnaires.

2.2.1. Self-ratings of "liking" and "wanting" for foods

In this task, 20 food pictures were presented and participants were asked to respond to the questions: (1) "How tasty is this food for you?" (*Liking*) and (2) "How much do you want this food now"? (*Wanting*). The experimenter indicated patients' responses on a 100 visual analogue scale anchored at each end with "not at all" and "extremely" [17]. In addition, participants were also asked the question: "How often do you eat this food?" Foods normally not eaten (Frequency: 0–10) were removed from the analysis. On average 9.35% of food items were removed for each patient.

2.2.2. Liking: affective priming task

Participants were instructed that they would see a picture (prime), followed by a smiley symbol (target), and that their task was to indicate whether the smiley was a positive or negative one, by pressing the marked keys (see Ref. [18]). Participants were instructed to not pay attention to prime stimuli and to respond as quickly and accurately as possible. The prime stimuli were 20 food pictures and 10 food-unrelated filler pictures (e.g., a comb, a hanger, a wardrobe, etc.) used as filler. The target stimuli were a positive and a negative emoticon (☺ and ☹).

The allocation of responses (positive/negative) to the response buttons was counterbalanced among participants. RTs on trials with errors or RTs below and above 2SD were excluded from the analyses. Each trial consisted of 250 ms prime period, a blank screen of 50 ms, resulting in a stimulus onset asynchrony (SOA) of a 300 ms, a target (which remained on screen until a response was given), and an intertrial interval period of 1500 ms. Each of the prime was presented twice (once followed by the negative target and once followed by the positive one), resulting in 60 trials. In order to determine participants' attitude, a positivity index was constructed for each item type by subtracting from the RTs for negative emotions the RTs for positive emoticons. Thus, lower values of this index indicate a more negative attitude. Stimulus presentation and data collection were accomplished using the E-prime software installed on a desktop computer.

2.2.3. Wanting: grip-force task

Participants were instructed that they would see reward pictures and that their task was to squeeze the handgrip proportionally to how much they want the stimuli (see Ref. [19]). The stimuli were pictures depicting primary rewards (foods) and, as a control condition, secondary rewards (six different amounts of euro coins: 1cent-1 euro). Every trial began with a fixation point (+) for 5000 ms, followed by the picture of the reward for 3500 ms. The inter-trial interval was 5000 ms. All trials were presented in a random order. There were two blocks of 13 trials each. Prior to the task, we collected a baseline measure for the hand dynamometer and the participant's maximal effort (MVC) (see Ref. [20]). This procedure was used to control for individual differences in strength. To analyze handgrip-force, we extracted in every trial the maximum or peak force exerted, which was expressed as a percentage of the MVC. Stimulus presentation was programmed on a PC using Psychopy v1.8, connected to a hand dynamometer of a Biopac™ system measuring handgrip-force.

2.2.4. Stimuli

The visual stimuli used were high-quality 20 colored photographs depicting food items and 10 photographs depicting food-unrelated items. More in detail, we selected 10 sweet and 10 salty food items, among those more frequently consumed by an independent sample of PD patients [17]. The same 20 food visual stimuli were used in each of the three experimental tasks. Sweet and salty foods were matched according to their frequency of consumption and tastiness.

2.3. Clinical and neuropsychological evaluation

All participants filled the Barratt Impulsiveness Scale (BIS-11), the Behavioral Inhibition & Activation Scales (BIS/BAS), and the Hospital Anxiety and Depression Scale (HADS). In addition, participants completed Mini Mental State Examination (MMSE), Frontal Assessment Battery (FAB), Semantic Verbal Fluency test, Trail Making Test (TMT), Attentive Matrices, Digit Span Forward, Rey's 15-word test and Poppelreuter-Ghent Test.

2.4. Statistical analysis

Data were analyzed using Statistica 7.0 (StatSoft, USA) software. Parametric and non-parametric tests were used where appropriate. Shapiro-Wilk test was undertaken to demonstrate that data were normally distributed. More in detail, for demographic, clinical, questionnaire and neuropsychological measures, comparisons between groups (e.g., PD + BE vs PD, PD + BE vs C, and PD vs C) were performed using independent samples t tests or Mann–Whitney *U* test. Gender distribution was analyzed using $\chi 2$ test.

Self-ratings of "liking", "wanting" and grip-force task were analyzed using repeated-measures analyses of variance (ANOVA). For self-ratings, food (sweet/salty) was the within-subjects variable. For grip-force task, reward (sweet-foods/salty-foods/money) was the within-subjects variable. Group (PD + BE/PD/C) was the between-subjects variable in all analyses. For the affective priming task, comparisons between groups were performed using Mann–Whitney *U* test. Spearman's rho correlation was used to examine the relationship between demographic, clinical, questionnaire, neuropsychological and behavioral measures.

3. Results

3.1. Demographic and clinical data

PD + BE, PD and C were matched for gender, age and education. Importantly, PD + BE had a significantly higher BMI compared to PD and C (see supplementary information). Finally, PD + BE, PD and C participants did not significantly differ on subjective ratings of hunger and fasting ($p > 0.5$).

Patient groups did not significantly differ from each other on disease duration [$t(29) = 1.06$, $p = 0.30$], UPDRS-III score [$t(27) = 1.44$, $p = 0.16$], H&Y score ($U = 98$, $Z = 0.30$, $p = 0.77$), LED total [$t(29) = 0.9$, $p = 0.38$], LED -Dopamine agonists (LED-DA; $U = 94$, $Z = -1.03$, $p = 0.30$) and LED Levodopa [$t(29) = 1.39$, $p = 0.17$].

The PD + BE group scored significantly higher, compared to the PD group, on the QUIP-RS sub-scale for eating, buying, hobbyism and total QUIP-RS score (all $ps < 0.01$). Instead, they did not differ for gambling, hyper-sexuality, punding and compulsive medication use sub-scales (see supplementary material).

3.2. Questionnaires and neuropsychological data

PD + BE scored significantly higher on HADS sub-scale of depression compared to PD ($U = 60.5$, $Z = 2.16$, $p = 0.03$) and C ($U = 90.5$, $Z = 1.98$, $p = 0.05$), which did not differ from each other ($U = 150$, $Z = 0$, $p = 1$).

Moreover, PD + BE scored lower, compared to C on the BAS fun-seeking sub-scale while no differences were found between the PD + BE and PD, and between PD and C. PD + BE scored lower compared to C on the FAB and Semantic Fluency test, while they scored lower compared to PD on Digit Span. No other significant results emerged (for more details on statistics see supplementary material). See Table 1 and Table S2.

3.3. Self-ratings of "liking" and "wanting" for foods

The ANOVA on "liking" ratings did not show significant results ($ps > 0.40$) (Fig. 1a). The same ANOVA on wanting ratings showed a main effect of type of food ($F_{1,\ 48} = 14.60$, $p < 0.001$), with sweet foods wanted more (mean ± SD: 31.56 ± 17.80) relative to salty foods (mean ± SD: 23.64 ± 17.40) (Fig. 1b). No significant differences between groups emerged ($ps > 0.40$).

3.4. Affective priming task

Participants did not differ on affective priming scores associated with salty foods (PD + BE vs PD: $U = 94$, $Z = -0.16$, $p = 0.87$; PD + BE vs C: $U = 130$, $Z = 0$, $p = 1$; PD vs C: $U = 141$, $Z = 0.30$, $p = 0.76$). However, PD + BE showed lower affective priming scores for sweet foods compared to C ($U = 59$, $Z = -2.62$, $p < 0.01$), while no differences were found between PD + BE and PD ($U = 75$, $Z = -1.04$, $p = 0.30$) and between PD and C ($U = 98$, $Z = -1.73$, $p = 0.08$) (Fig. 2a). Importantly, participants did not differ on affective priming scores in the control condition, when food-unrelated filler pictures were presented (PD + BE vs PD: $U = 66$, $Z = -1.45$, $p = 0.15$; PD + BE vs C: $U = 93$, $Z = -1.36$, $p = 0.17$; PD vs C: $U = 128$, $Z = 0.73$, $p = 0.46$).

3.5. Grip-force task

The ANOVA group (PD + BE, PD, C) x reward (sweet foods, salty foods, money) showed a significant main effect of reward ($F_{2,\ 96} = 17.04$, $p < 0.0001$). Post hoc analysis showed that the participants' hand-grip force for sweet and salty foods was higher relative to money items ($Ps > 0.0001$) (Fig. 3a). No other significant results emerged ($Ps > 0.29$).

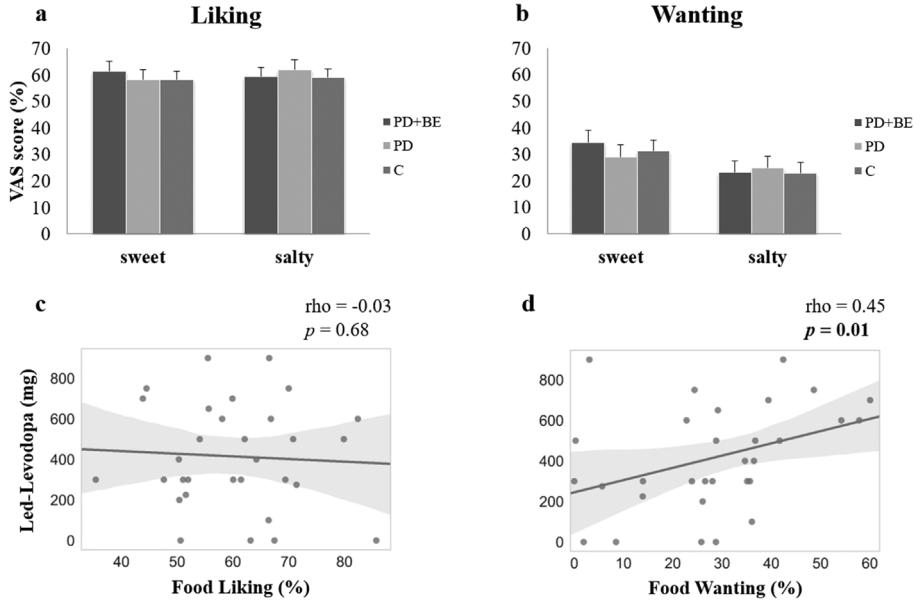

Fig. 1. (a) Mean self-ratings of Liking and (b) Wanting for sweet and salty foods for PD + BE, PD and C participants. (c) Correlations between LED-Levodopa and food Liking and (d) Wanting across all PD participants. The error bar represents standard error.

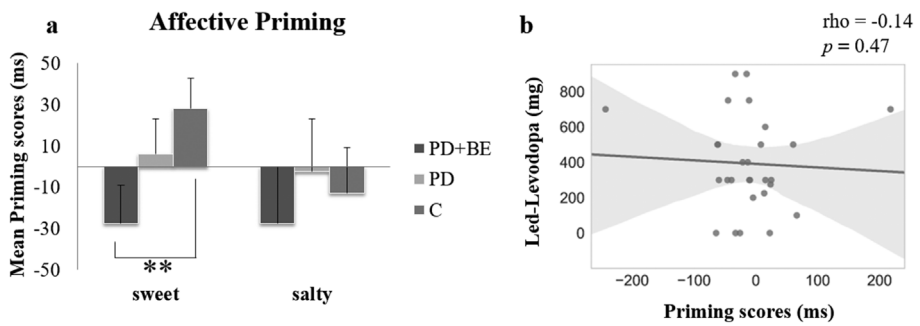

Fig. 2. (a) Mean affective priming scores for sweet and salty foods for PD + BE, PD and C participants. (b) Correlation between LED-Levodopa and affective priming scores for food overall across all PD participants. The error bar represents standard error.

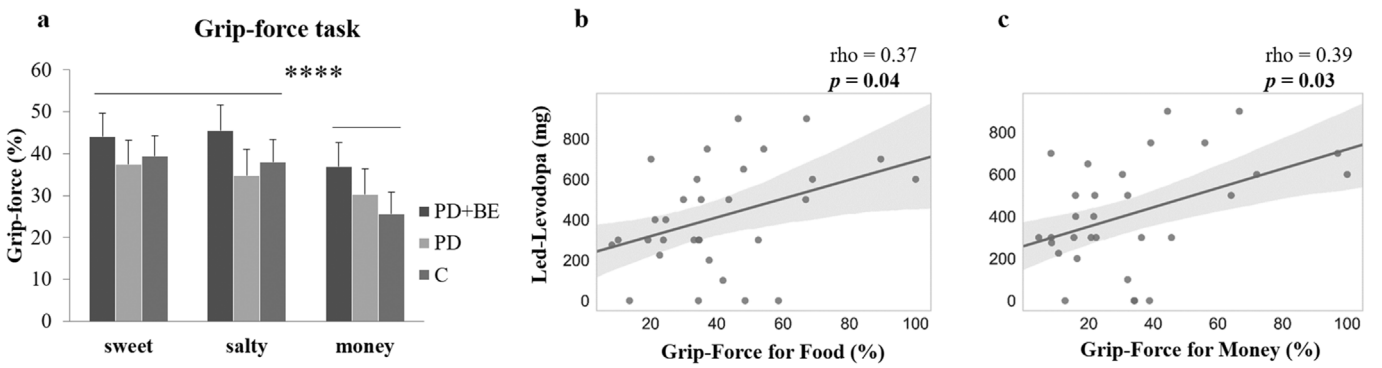

Fig. 3. (a) Mean grip-force scores for sweet/salty foods and money for PD + BE, PD and C participants. (b) Correlation between LED-Levodopa and grip-force scores for food overall across all PD participants. (c) Correlation between LED-Levodopa and grip-force scores for money across all PD participants. The error bar represents standard error.

3.6. Correlational analysis

3.6.1. Binge eating

Across all PD patients the QUIP-RS sub-scale for *binge eating* negatively correlated with Digit Span Forward scores (rho = −0.43, $p = 0.01$) and positively correlated with the HADS sub-scale for depression (rho = 0.47, $p < 0.01$). No significant correlations were found between binge eating scores and LED-levodopa, LED-DA or LED total or other measures (see supplementary material).

3.6.2. LED

We found a positive correlation between LED-Levodopa and self-ratings of "wanting" (rho = 0.45, $p = 0.01$) (Fig. 1d) but not "liking" (rho = −0.03, $p = 0.86$) for food overall (Fig. 1c). In the same way, LED-Levodopa positively correlated with the hand-grip force for both food (rho = 0.37, $p = 0.04$) (Fig. 3b) and money (rho = 0.39, $p = 0.03$) (Fig. 3c), but not with affective priming scores for foods (Fig. 2b) and non-food items ($Ps > 0.47$). Conversely, LED-DA negatively correlated with the hand-grip force for food and money (respectively, rho = −0.49, $p < 0.01$; and rho = −0.57, $p < 0.001$).

4. Discussion

This study explored whether BE in PD patients is associated with increased incentive salience for food rewards. We found that patients with BE displayed an altered liking for sweet foods but not increased wanting. Importantly, this difference emerged only when implicit measures were used, while no differences emerged in self-report ratings of liking and wanting. Liking was measured with an affective priming task that assesses participants' attitudes and affective reactions in a relatively automatic way, without the need for conscious reflection (see Ref. [21]). In this task, patients with BE showed a negative attitude toward sweet foods compared to controls. This result seems in line with studies reporting a less positive attitude for palatable foods in individuals with eating alterations, such as, for instance, restraint eaters [18]. As it happens in unsuccessful dieters, sweet foods pose a particular challenge on PD patients with BE. Indeed, as reported by Ref. [22], patients with ICDs frequently report preoccupations, the inability to control the urges or impulses, and other pathological behaviors (such as lying or stealing) that arise to act on these urges. This result is also consistent with studies reporting a preference for sweet foods in patients with PD [23]. However, this result must be interpreted with caution since no difference was observed between PD patients with and without BE. The method we used to identify binge eaters may explain this null result. As mentioned in the limitation section, the QUIP has indeed two main limitations: first, it lacks validation in the Italian population, and second, it is a self-report measure. For these reasons, it may not be able to identify more subtle disorders. Of course, these are speculations and future studies are warranted in order to investigate these aspects.

In our study, patients with BE did not report increased wanting for food. This is at variance with several studies reporting increased ventral striatal dopamine responses in ICDs to rewards-related cues, consistently with a global sensitization to appetitive behaviors [4–7] (see Ref. [5] for a different finding). Two main considerations can be advanced. First, it is possible that our tasks fail to capture eventual alterations in food incentive salience. This is in line with the concerns already present in the literature about the possibility to disentangle liking and wanting in humans with behavioral tasks [24]. Crucially, in our study we found that LED-levodopa significantly correlated with the performance in tasks assessing wanting (both in the self-report measure and in the handgrip force task) and not with liking tasks. These results, that are consistent with the Incentive sensitization theory [8], suggest that the tasks we used are able to capture the wanting component. Second, it is possible that BE in PD patients is preferably associated with altered liking for rewards or, more in general, with affective abnormalities. Interestingly, we found an association between binge eating and depression, in accordance with previous studies on ICDs [25]. More in general, our results are, at least in part, more in line with other theories of addiction, as for instance the reward deficiency syndrome (RDS) theory [26]. According to this theory, individuals with addictive behaviors exhibit a chronic hypoactivation of brain reward pathways and a reduced pleasurable experience from rewards. Importantly, addictive behaviors are believed to emerge in order to compensate for this deficiency and stimulate brain reward areas. This hypothesis has recently been extended also to the food domain [27]. More studies are thus necessary in order to clarify this issue, since this is the first study in which reward sensitivity has been investigated in patients with BE.

Interestingly, binge eaters PD patients presented lower working memory (WM) scores compared to non-binge eaters patients. Indeed, deficits in executive functions, including working memory, have been proposed as potential responsible of the phenomenology of ICDs and have been frequently reported [10]. Moreover, WM is also one of the executive functions that have been associated with eating behaviors. More in details, WM is believed to allow individuals to maintain long-term outcome (such for instance, a healthy diet) and avoid to pursue non in line short-term goals [28]. An enhanced general susceptibility to cognitive interference of WM in the context of salient food cues has been reported for instance in studies on BE in the general population [29].

Lastly, some limitations of the study should be addressed. First, we used the QUIP-RS questionnaire instead of a clinical psychiatric assessment to distinguish PD patients with and without ICDs. Moreover, this questionnaire still lacks a validation on the Italian population. Second, differently from what observed with LED-levodopa, a negative correlation between LED-DA and the grip force task assessing wanting was obtained. Although both levodopa and dopamine agonists stimulate dopamine receptors, they have different pharmacokinetic characteristics, which may explain this result; moreover, dopamine agonists also differ between each other [30].

In conclusion, our results showed that binge eating in PD is associated with cognitive abnormalities, and to lesser extent affective abnormalities, but not with increased incentive salience. More studies are necessary in order to further understand the mechanisms underlying BE in PD. This aim is particularly important considering that this disorder not only affects patients' lives, but also it exposes them to negative health outcomes.

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Abbreviations

BE: Binge eating
ICDs: Impulse control disorders
fMRI: Functional Magnetic Resonance Imaging
PET: Positron Emission Tomography
C: Healthy Controls
QUIP-RS: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale
BIS-11: Barratt Impulsiveness Scale
LED: L-dopa equivalent dose
MMSE: Mini- Mental State Examination
HADS: Hospital Anxiety and Depression Scale
BMI: Body Mass Index
MSA: Dopamine dysregulation syndrome
PD: Parkinson's disease
BIS/BAS: Behavioral Inhibition & Activation Scales
H&Y: Hoehn and Yahr scale
UPDRS-III: Motor section of the Unified Parkinson's Disease Rating Scale
FAB: Frontal Assessment Battery
TMT: Trail Making Test
WM: Working Memory