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ORIGINAL COMMUNICATION

Deep brain stimulation of the subthalamic nucleus and the temporal discounting of primary and secondary rewards

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Abstract
Although deep brain stimulation of the subthalamic nucleus is an effective surgical treatment for Parkinson's disease, it may expose patients to non-motor side effects such as increased impulsivity and changes in decision-making behavior. Even if several studies have shown that stimulation of the subthalamic nucleus increases the incentive salience of food rewards in both humans and animals, temporal discounting for food rewards has never been investigated in patients who underwent STN-DBS. In this study, we measured inter-temporal choice after STN-DBS, using both primary and secondary rewards. In particular, PD patients who underwent STN-DBS (in ON medication/ON stimulation), PD patients without STN-DBS (in ON medication) and healthy matched controls (C) performed three temporal discounting tasks with food (primary reward), money and discount vouchers (secondary rewards). Participants performed also neuropsychological tests assessing memory and executive functions. Our results show that STN-DBS patients and PD without DBS behave as healthy controls. Even PD patients who after DBS experienced weight gain and/or eating alterations did not show an increased temporal discounting for food rewards. Interestingly, patients taking a higher dosage of dopaminergic medications, fewer years from DBS surgery and, unexpectedly, with better episodic memory were also those who discounted rewards more. In conclusion, this study shows that STN-DBS does not affect temporal discounting of primary and secondary rewards. Furthermore, by revealing interesting correlations between clinical measures and temporal discounting, it also shed light on the clinical outcomes that follow STN-DBS in patients with PD.

Keywords Parkinson's disease · Temporal discounting · Food reward · Deep brain stimulation · Subthalamic nucleus

Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective and widely used treatment for motor symptoms in Parkinson disease (PD). DBS is a safe procedure but can be associated with adverse events, affecting cognition, emotions, and behavior [1]. These effects are dependent mainly on the electrode placement within the STN and the spread of stimulation to its associative and limbic territories and to the reduction in anti-parkinsonian drug dose [1]. However, even the surgical procedure and, in particular, the micro-lesions associated with electrodes implantation, may contribute to such deficits [2–4].

Increased impulsivity and changes in decision-making behavior have been frequently observed, although not consistently, after STN-DBS in PD patients [5, 6]. For instance, patients treated with DBS have been shown to exhibit a tendency towards risky decision-making in gambling tasks and high rates of errors and failure to inhibit prepotent and habitual responses in choice reaction time paradigms such as the Go/No-Go task, the Stroop task, and the Stop-signal task. Moreover, psychiatric problems such as obsessions and compulsions and new-onset impulse control disorders have also been reported [5, 6]. Patients may even show increased impulsivity in personality trait assessments [7].

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Delay discounting is a task typically used to assess decisional impulsivity. In this task, participants are asked to decide whether they prefer an immediate, smaller reward over a larger, delayed one [8]. What is usually observed is that, when the temporal delay is very short, individuals select the large reward but as the temporal delay increases, they become less likely to select the large, delayed reward. The more participants result impulsive the more they prefer immediate rewards over delayed ones. Delay discounting of monetary rewards has been shown to be enhanced in PD-DBS in one study [9] but two other studies that have investigated the same issue have found no effect of STN-DBS on decisional impulsivity [10, 11]. Conversely, in rats, lesions of the STN have been found to decrease delay discounting [12].

Notably, studies on patients have all employed tasks assessing discounting of a secondary reward, that is, money. It is interesting to note that high-frequency stimulations of the STN in rats have been shown to increase motivation to obtain primary rewards (i.e., food) and to reduce motivation toward secondary rewards [i.e., drugs; 13]. In line with this evidence, some studies have shown an increased attribution of incentive salience to rewarding food stimuli in PD patients after STN-DBS and its association with weight gain, a frequently observed non-motor side effect of STN-DBS [13–15].

Thus, to extend the current knowledge about the impulsive behavior after STN stimulation and to shed light on the complex clinical outcomes that follow STN-DBS in patients with PD, in this study we investigated inter-temporal choices after STN-DBS for both primary (i.e., food) and secondary rewards (i.e., money and discount vouchers) in a sample of PD patients treated with STN-DBS, PD patients without DBS and healthy controls (C).

Methods

Participants

A total of 45 participants took part in the study: 15 patients with PD treated with STN-DBS (DBS+), 15 patients with PD without DBS under dopaminergic replacement therapy (DBS−), and 15 healthy controls (C). PD patients treated with STN-DBS were referred to the neurology unit of "Santa Maria della Misericordia" University hospital in Udine. They were chronically stimulated by bilateral STN-DBS (mean years from DBS = 4.4 years, SD = 2.06, range 1–7 years). The parameters of stimulation were the following: mean voltage 2.53 mA (SD = 0.45) for the right side and 2.37 mA (SD = 0.38) for the left side; mean impulse duration 58.13 msec (SD = 7.79) for the right side and 60.13 msec (SD = 16.04) for the left side; mean frequency 137.2 Hz (SD = 27.12) for the right side and 137.2 Hz (SD = 27.12) for the left side. Mean levodopa equivalent daily dose (LED) was 851.8 (SD = 530.9).

PD patients under dopaminergic replacement therapy were referred to the neurologic unit of the "Santa Maria della Misericordia" University hospital in Udine and Cattinara University hospital in Trieste. Healthy individuals had no history of neurological disease, head injury or alcohol abuse and displayed no signs of dementia. All participants were screened for cognitive status using the Mini-Mental State Examination [MMSE, 16]. No significant differences were found in age, education or MMSE, among the three groups [Age, $F_{(2, 42)} = 2.68$ $p = 0.08$; Edu, $F_{(2, 42)} = 2.42$ $p = 0.10$; MMSE, $F_{(2, 42)} = 1.92$ $p = 0.16$]. Moreover, PD patients with STN-DBS and PD patients without STN-DBS did not differ in UPDRS motor score part III [$t = -1.51$ $p = 0.14$], see Table 1. All patients were tested under their best medical treatment condition (i.e., ON stimulation/ON medication for DBS+, and ON medication for DBS−).

Clinical evaluation

All patients were diagnosed using the Unified Parkinson's Disease Rating Scale (UPDRS)—Part III. Apart from the Mini-Mental State Examination [MMSE, 16], the Frontal Assessment Battery [FAB, 17] and the Digit span task [18] were administered to all participants. In addition, patients also performed the Phonological and Semantic Verbal Fluency tests [19], Corsi span task [18], Rey's 15-word test-immediate recall and delayed recall [20]. Data were corrected for age and educations. Table 1 summarizes demographical and clinical information about participants.

Temporal discounting task

Participants performed three computerized temporal discounting tasks in which they made choices between an amount of reward that could be received immediately (immediate option) and an amount of reward that could be received after some specific delays (delayed option). We used a procedure similar to that used by Sellitto et al. [21]. The task included six delays: 2 days, 2 weeks, 1 month, 3 months, 6 months, and 1 year. All rewards were hypothetical. For what concerns the food task, participants were asked to choose their preferred food from a selection of six foods selected from a database developed in our lab (Foroni et al. in preparation). Three were sweet food and three were salty foods (see Fig. 1, A). Similarly, for what concerns discount voucher, participants were asked to choose their preferred option among six pleasurable hobbies/activities presented through pictures (i.e., going to the theater, buy books, going to the restaurant, buy gardening equipment, buy sewing tools and buy tools to paint) for which they would desire to obtain

Table 1 Parkinson's disease patients and controls—demographic and disease characteristics

	DBS+ Mean (SD)	DBS− Mean (SD)	C Mean (SD)	*p*
Age (years)	62.8 (7.2)	69.1 (7.76)	67.7 (8.3)	0.08
Education (years)	12.5 (4.7)	9.3 (4.2)	10.3 (3.1)	0.10
Disease duration (years)	13.9 (5.3)	8.73 (3.51)	–	**0.003**
Years from DBS	4.4 (2.06)	–	–	–
UPDRS motor score part III[a]	11 (5.62)	15.4 (9.7)	–	0.14
MMSE	29.13 (0.91)	28. 2 (2.1)	29.1 (1.1)	0.16
FAB	13.5 (3.03)	15.4 (1,9)	16. 8 (1.5)	**< 0.001***
DIGIT	5.14 (0.82)	5.40 (0.9)	6.25 (1.04)	**< 0.005****
CORSI	4.6 (0.96)	4.9 (1.4)	–	0.44
Rey's 15-word test-IR	38.1 (9.19)	45.4 (9.65)	–	**0.04**
Rey's 15-word test-DR	7.73 (3.28)	9.4 (3.2)	–	0.17
Phonemic fluency	30.9 (15.5)	33.5 (7.9)	–	0.57
Semantic fluency	40.4 (9.5)	41.1 (12.12)	–	0.86

Significant *p* values are shown in bold

IR immediate recall, *DR* delayed recall

[a]UPDRS-III in ON medication/ON stimulation in DBS+; ON medication in DBS−

*DBS + vs DBS- $p=0.02$; DBS + vs C $p=0.0002$; DBS-vs C $p=0.08$

**DBS + vs C $p=0.002$; DBS-vs C $p=0.01$; DBS + vs DBS− $p=0.45$

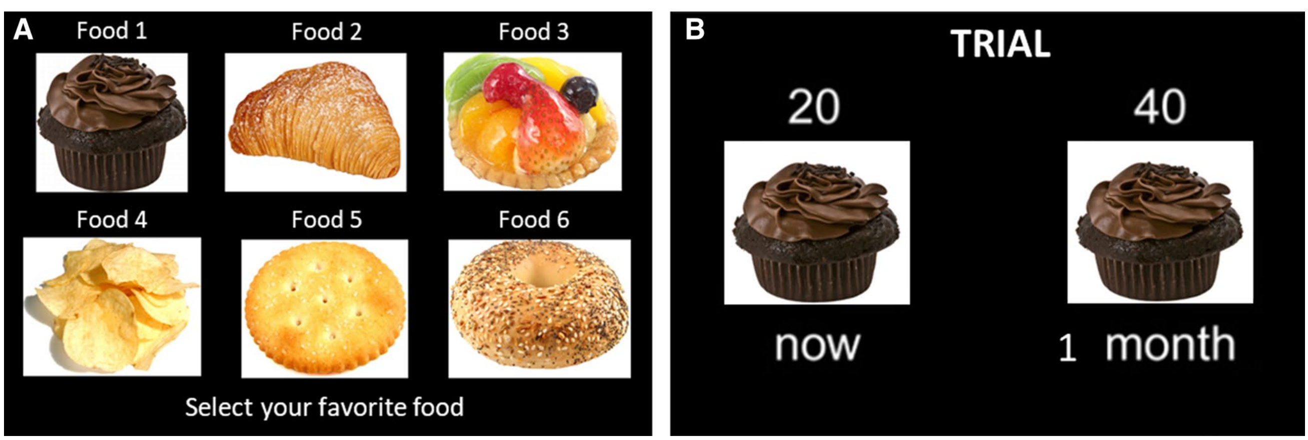

Fig. 1 Food temporal discounting task. **a** Food options. **b** Example of a trial used in the task

discount voucher. As in Sellitto et al. [21], the selected food and discount voucher were used as rewards in the food and discounting voucher task (example provided in Fig. 1b).

Data analysis

Data were analyzed using Statistica 8.0 (StatSoft, USA) software. Parametric and non-parametric tests were used where appropriate. Kolmogorov–Smirnov test was undertaken to demonstrate that data were normally distributed. We compared groups on clinical and demographical data. For the temporal discounting task, we first computed the area under the curve (AUC) (the smaller this area, the more the subject's discount rewards) and then we performed a Kruskal–Wallis ANOVA on AUC values. Second, we assessed which of two different models (hyperbolic and exponential) fit the data better by focusing on R^2 scores [22]. An ANOVA on log-transformed k estimates values was then performed with group and reward as factors. The relationship between task performance and disease characteristics (disease duration, motor symptoms, neuropsychological performance) was investigated in exploratory correlations using the Spearman's rank coefficient. Finally, using medical records, we divided PD patients who underwent STN-DBS into two groups: those who experienced weight gain and/or eating alterations after surgery and those who did not experience these adverse effects and we compared the two groups in the temporal discounting tasks by Mann–Whitney *U* test.

Results

A Kruskal–Wallis ANOVA on AUC values with group (DBS+, DBS−, C) as factor showed no significant differences when we considered food [H (2, 45) = 2.26 p = 0.32], hobby [H (2, 45) = 1.11 p = 0.57] and money [H (2, 45) = 3.87 p = 0.14]. A Friedman ANOVA showed significant differences between the type of rewards [F (45, 2) = 14.99 $p < 0.001$]. Food was discounted more than hobby (Wilcoxon, $p < 0.01$) and money (Wilcoxon, $p < 0.001$), while no difference was observed between money and hobby (Wilcoxon, p = 0.69). See Fig. 2 for AUC values distributions in the three groups.

The comparison among hyperbolic and exponential discounting models showed that the hyperbolic model fitted the data better than the other model across rewards and groups (see Table 2). This suggests that participants discounted rewards hyperbolically, rather than exponentially.

An ANOVA on *k* values showed a significant main effect for reward [F (2,84) = 7.34 p = 0.001]. No main effect of group [F (2,42) = 0.68 p = 0.50] and no interaction group x reward [F (4,84) = 0.38 p = 0.81] were observed.

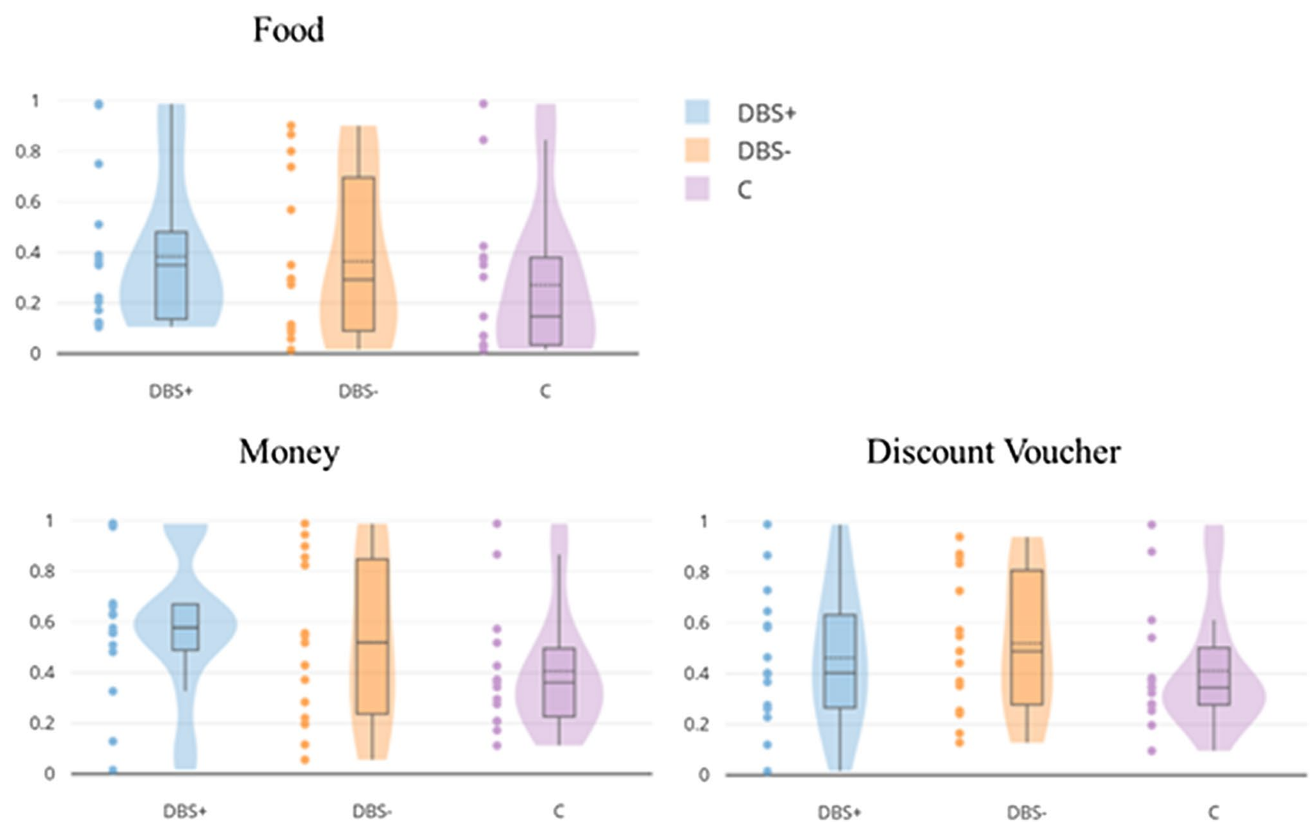

Fig. 2 AUC violin plots for patients DBS+, patients DBS−, and C (n = 45). Dashed lines represent mean values for each group. The boxes represent the third (top) and first (bottom) quartiles. The band represents the second quartile (median). The whiskers represent the range of data (minimum and maximum). The shaded areas represent the frequency of individuals with corresponding AUC values. The distribution of AUC values was plotted using the Plotly package (https://github.com/ropensci/plotly; http://plot.ly)

Table 2 Hyperbolic and exponential parameter values for each of the reward and for each group

	Food		Hobby		Money	
	Hyperbolic	Exponential	Hyperbolic	Exponential	Hyperbolic	Exponential
DBS+	0.6	0.4	0.6	0.4	0.8	0.7
DBS−	0.7	0.4	0.8	0.6	0.8	0.7
C	0.8	0.6	0.6	0.3	0.7	0.4
Overall	0.7	0.5	0.7	0.4	0.8	0.6

Correlational analyses

When we considered AUC values in DBS+ patients, we observed a significant inverse correlation between AUC values for money and Rey word recall (rho = − 0.56 p = 0.03) meaning that individuals with better episodic memory were also those who selected immediate monetary rewards. Moreover, AUC values for money significantly correlated with years from DBS surgery (rho = 0.69 p = 0.004): the lower the time from surgery, the higher the preference for immediate monetary rewards. Interestingly, we also found a significant correlation between AUC values for food and LED scores (rho = − 0.53 p = 0.041): the higher the LED scores, the higher the preference for immediate food rewards. No significant correlations were observed between AUC values and UPDRS ON scores (all $ps > 0.17$).

When we considered DBS− patients, we only observed a significant correlation between AUC values for food and digit span (rho = − 0.61 p = 0.01): as observed in the DBS+ group, patients with a higher digit span (i.e., higher memory performance) were also those who prefer more immediate food rewards. No correlations were observed with disease duration ($ps > 0.10$) or UPDRS ($ps > 0.47$), or LED ($ps > 0.42$).

Intergroup analyses

We then considered patients who developed weight gain and/or eating alterations after DBS-STN compared to those who did not experience these adverse effects. The two groups (DBS+ BMI+, $n = 6$ and DBS+BMI−, $n = 9$) did not differ in clinical and demographical characteristics (all $ps > 0.28$). When we considered AUC values, no significant differences emerged for each of the three rewards [food ($U = 14$ $p = 0.12$); discount voucher ($U = 26$ $p = 0.90$); money ($U = 22.5$ $p = 0.59$)], see Fig. 3.

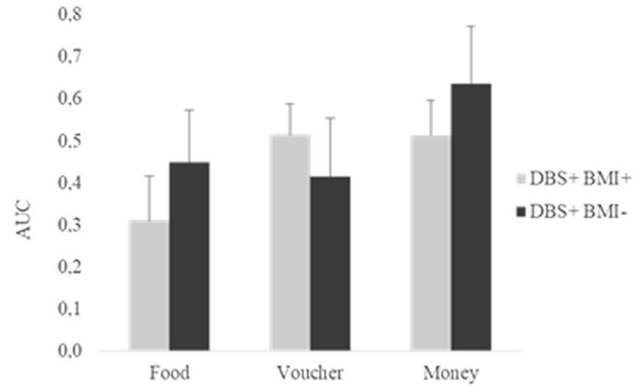

Fig. 3 The area under the discounting curve (AUC) by participant group and type of reward. The error bars represent SEM

Discussion

The study shows that PD patients who underwent STN-DBS surgery did not discount rewards more than PD patients without STN-DBS and healthy controls. This result confirms previous investigations showing no difference between ON and OFF STN-DBS on delay discounting in PD patients [9–11, but see 9]. In addition, our results also extend the current literature by showing, for the first time, that this result is independent of the type of reward (primary vs secondary rewards). Our hypothesis that PD patients with STN-DBS may experience increased decisional impulsivity toward food was based on the observation that lesions or stimulations of the STN increase motivation to obtain food rewards in both animals [23, 24] and humans [25]. Despite this evidence, no difference emerged even when PD patients with STN-DBS who have experienced weight gain and eating alterations after surgery were compared to those who did not experience these adverse effects.

As a matter of fact, impulsivity encompasses a wide range of behaviors, from motor disinhibition to altered decision-making [26]. Even if the detrimental effects of STN-DBS on motor disinhibition have been frequently described and attributed to the STN's role in pausing the motor system in decision conflicts [27], it may exert different effects or no effects on decisional impulsivity in PD patients. It has been shown that, in both rats and humans, impulsive choice and impulsive action do not correlate, and that they may be supported by different neural substrates [28]. Of course, results may be also driven by the small size of our samples, and studies on larger series are needed to clarify whether STN stimulation may, for instance, affect differentially decisional impulsivity in PD patients according to the cognitive status, salience attributed to rewards and preferences.

Interestingly, we observed that shorter time from surgery, higher LED and, surprisingly, better memory were associated with higher discounting rates of rewards. The observation that shorter time from surgery and higher LED are associated with increased impulsivity is in line with the literature. For instance, a recent study assessing 69 PD patients after 6 years of stimulation reports an improvement of impulse control disorders and neuropsychiatric fluctuations [29]. In addition, it has been shown that the pharmacological enhancement of dopamine activity through L-DOPA administrations increase delay discounting in healthy participants [30]. More controversial is the result concerning memory and delay discounting. Although valuation of future rewards has been shown to be associated with memory processes, such as working memory, episodic future thinking and episodic memory [e.g., 31, 32], it has usually been shown that participants with better episodic and working memory demonstrated less severe discounting of rewards [e.g., 33]. Our result is difficult to be explained. We may speculate that the characteristics of our participants may have driven it. For instance, it has recently been shown that memory decline is associated with different choice preferences in elderly males and females in delay discounting tasks: while men with higher memory scores show less delay discounting, women with higher memory scores tended to discount reward more. Although this argument may not account for our data (more men than women in our groups), it suggests that individual differences may exist when making inter-temporal decisions.

Finally, we are aware that our study has several limitations. First, the food temporal discounting task that we used lacks ecological validity. Other studies have tried to overcome this limitation by asking, for instance, participants to decide between a different number of bites of a certain food rather than the whole food [e.g., 34]. It would be interesting in the future to use this type of paradigm also with patients with PD. Second, we did not assess the presence of impulse control disorder in our patients with a quantitative measure. This may have had us to better characterize the patient's sample. Finally, we did not assess patients in OFF and ON stimulation. This double testing is generally used to control for the effect of surgery. However, we were specifically interested in investigating whether PD patients with STN-DBS were more impulsive than patients without and healthy controls.

In conclusion, this study shows that STN-DBS does not affect temporal discounting of primary and secondary rewards. Furthermore, by revealing interesting correlations between clinical measures and temporal discounting, it also sheds light on the clinical outcomes that follow STN-DBS in patients with PD.

Compliance with ethical standards

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical standards All participants gave written informed consent to participate in the study that was approved by SISSA Ethics Committee and has, therefore, been performed in accordance with the ethical standards of the Declaration of Helsinki.

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