J Neurol (2015) 262:1541–1547
DOI 10.1007/s00415-015-7749-9

ORIGINAL COMMUNICATION

Deep brain stimulation of the subthalamic nucleus modulates reward processing and action selection in Parkinson patients

Caroline Wagenbreth[1] · Tino Zaehle[1] · Imke Galazky[1] · Jürgen Voges[1,2] · Marc Guitart-Masip[3,4] · Hans-Jochen Heinze[1,2] · Emrah Düzel[5,6,7]

Received: 5 March 2015 / Revised: 11 April 2015 / Accepted: 12 April 2015 / Published online: 1 May 2015

Abstract Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective treatment for motor impairments in Parkinson's disease (PD) but its effect on the motivational regulation of action control is still not fully understood. We investigated whether DBS of the STN influences the ability of PD patients to act for anticipated reward or loss, or whether DBS improves action execution independent of motivational valence. 16 PD patients (12 male, mean age = 58.5 ± 10.17 years) treated with bilateral STN-DBS and an age- and gender-matched group of healthy controls (HC) performed a go/no-go task whose contingencies explicitly decouple valence and action. Patients were tested with (ON) and without (OFF) active STN stimulation. For HC, there was a benefit in performing rewarded actions when compared to actions that avoided punishment. PD patients showed such a benefit reliably only when STN stimulation was ON. In fact, the relative behavioral benefit for go for reward over go to avoid losing was stronger in the PD patients under DBS ON than in HC. In PD patients, rather than generally improving motor functions independent of motivational valence, modulation of the STN by DBS improves action execution specifically when rewards are anticipated. Thus, STN-DBS establishes a reliable congruency between action and reward ("Pavlovian congruency") and remarkably enhances it over the level observed in HC.

Keywords Parkinson's disease · Deep brain stimulation · Subthalamic nucleus · Action selection · Reward

C. Wagenbreth and T. Zaehle contributed equally.

✉ Tino Zaehle
tino.zaehle@ovgu.de

Caroline Wagenbreth
caroline.wagenbreth@med.ovgu.de

Imke Galazky
imke.galazky@med.ovgu.de

Jürgen Voges
juergen.voges@med.ovgu.de

Marc Guitart-Masip
marc.guitart-masip@ki.se

Hans-Jochen Heinze
heinze@med.ovgu.de

Emrah Düzel
emrah.duezel@dzne.de

[1] Departments of Neurology and Stereotactic Neurosurgery, Otto-von-Guericke University Magdeburg, 39120 Magdeburg, Germany

[2] Department of Behavioral Neurology, Leibniz Institute of Neurobiology, Magdeburg, Germany

[3] Wellcome Trust Centre for Neuroimaging, Institute of Neurology, University College London, London WC1N 3BG, UK

[4] Ageing Research Centre, Karolinska Institute, SE-11330 Stockholm, Sweden

[5] Institute of Cognitive Neurology and Dementia Research, Otto-von-Guericke-University Magdeburg, Magdeburg, Germany

[6] German Center for Neurodegenerative Diseases (DZNE), Site Magdeburg, Magdeburg, Germany

[7] Center for Behavioral and Brain Sciences, CBBS, Magdeburg, Germany

Introduction

Deep brain stimulation of the subthalamic nucleus (STN-DBS) has become a standard and effective treatment in advanced Parkinson's disease (PD). Although the mechanisms of DBS are still not sufficiently clarified, it is assumed that the high-frequency stimulation leads to a functional inhibition of the hyperactive STN and thereby reduces the inhibitory influence of the basal ganglia (BG) nuclei on thalamo-cortical projections [1] which—in consequence—leads to an overall improvement in motor functions.

While STN-DBS can lead to considerable motor improvements [1, 2], its effects on the motivational regulation of action control are still unclear and there is evidence to suggest that STN-DBS could influence the flexibility of instrumental behavior in the face of a motivational outcome. Goal-directed instrumental action control ideally entails the flexibility to deploy or withhold actions independent of whether the goal is to obtain reward or to avoid loss [3]. However, this flexibility is constrained by seemingly hard-wired congruencies (so-called "Pavlovian congruencies") that favor the performance of actions that lead to rewards and the inhibition of actions that lead to losses [4]. This asymmetry in choices is mirrored by the direct and indirect pathways of the striatum that reinforce rewarded actions or inhibit punished actions, respectively [5] and is modulated by dopamine [3, 4, 6, 7]. It has been suggested that the STN acts by increasing the decision threshold of actions encoded within the BG systems [8] when control over preponderant actions needs to be exerted [9]. Therefore, one possibility is that STN-DBS selectively releases the brake over Pavlovian congruent actions preferentially computed in the striatum resulting in advanced performance for reinforce rewarded actions and inhibit punished actions. Alternatively, STN-DBS will improve performance of any action regardless of Pavlovian congruency between action and reward and increased errors of commission on the no-go trials.

In the present study, we tested between these two alternatives. To that end, we adapted the Go/NoGo action/loss (or valenced Go/NoGo) paradigm [4, 10] to a simplified format that can be performed by PD patients. Patients were instructed to make actions to obtain rewards, to make actions to avoid losses, to withhold actions to obtain rewards and to withhold actions to avoid losses. Patients were tested in two conditions, with the STN-DBS being ON and OFF. We hypothesize that if STN-DBS selectively releases the brake over Pavlovian congruent actions, DBS ON will increase the advantage of performing instructed go actions to obtain rewards when compared to make actions to avoid losses.

Methods

Participants

The study included 16 patients with PD (12 male (75 %), mean age = 58.5 ± 10.17 years; 13 right handed) with bilateral DBS of the STN. Patients were recruited from the Departments of Neurology and Stereotactic Neurosurgery at the University of Magdeburg and the diagnosis of PD was confirmed by a neurologist specialized in movement disorders. The mean duration since DBS operation was 27.63 ± 24.51 months. Demographic and disease characteristics of each patient can be seen in Table 1. All patients remained on their prescribed dopaminergic medication in conjunction with DBS and were tested during the ON state of their medication cycle. All patients had chosen DBS surgery because their medications were no longer providing optimal control over their motor symptoms. Group DBS parameters at the time of testing were as follows: *voltage* (right: median = 2.8, range 1.0–5.8; left: median = 2.5; range 2.0–5.5), *frequency* (right: median = 130, range 60–200; left: median = 130; range 60–200) and *pulse width* (right: median = 60; range 60–130; left: median = 60; range 60–130). Individual parameters are listed in Table 1.

Electrodes were placed bilaterally in the STN of all patients. The surgical procedure for STN-DBS utilized standard stereotactic techniques with microelectrode recordings for electrophysiological localization and has been described previously [11]. The healthy control group (HC) consisted of 16 age- and gender-matched participants (mean age 58.38 ± 10.14 years, 12 male). None of the patients and controls fulfilled neuropsychological criteria for dementia or showed clinically relevant levels of depression at the time of testing. Further exclusion criteria were: history of neurological condition other than PD (for patients), any psychiatric condition known to compromise executive cognitive functioning (e.g., schizophrenia, bipolar affective disorder, mood disorders) or any untreated or unstable medical conditions. Also, patients only participated when they were able to execute simple finger movements to press a button when STN-DBS was OFF.

All patients and HC participated voluntarily and could quit the test at any times. Written informed consent was obtained from all patients and HC participating in the study and the experiment was approved by the local ethics committee (University of Magdeburg, Germany).

Stimuli

The experimental paradigm was generated and carried out with Presentation software (Neurobehavioral Systems,

Table 1 Demographic and disease characteristics in PD patients

Patient #	Age (years)	Gender	Disease duration (years)	Assessment post surgery (months)	LED (mg/day)	DBS contacts	DBS voltage (V), frequency (Hz), pulse width (μs)
1	60	F	23	12	528	10− G+/2− G+	3.0 V, 130 Hz, 60 μs/4.0 V, 130 Hz, 60 μs
2	72	M	10	66	1829	1− G+/6− G+	5.8 V, 130 Hz, 60 μs/2.0 V, 130 Hz, 90 μs
3	53	M	9	13	813	C+ 3−/C+ 11−	2.8 V, 130 Hz, 90 μs/2.0 V, 130 Hz, 90 μs
4	75	F	8	12	0	C+10−/C+ 2−	3.5 V, 130 Hz, 60 μs/4.0 V, 130 Hz, 60 μs
5	52	F	17	62	1664	2− G+/6− G+	3.2 V, 60 Hz, 90 μs/3.0 V, 60 Hz, 90 μs
6	68	M	11	52	157	3− G+/5− 7+	5.0 V, 130 Hz, 60 μs/3.5 V, 130 Hz, 60 μs
7	52	M	14	29	482	3− G+/10− 11+	1.0 V, 180 Hz, 60 μs/5.5 V, 180 Hz, 60 μs,
8	55	M	32	13	838	2− 1+/10− 11+	2.8 V, 130 Hz, 90 μs/2.2 V, 130 Hz, 90 μs
9	68	M		51	500	3+ 2−/7+ 6−	4.0 V, 130 Hz, 130 μs/4.0 V, 130 Hz, 130 μs
10	57	M	11	9	480	2− G+/11− G+	1.1 V, 60 Hz, 60 μs/3.6 V, 60 Hz, 60 μs
11	66	M	17	61	728	2− G+/4− 6+	2.0 V, 130 Hz, 60 μs/3.5 V, 130 Hz, 60 μs
12	64	F	10	49	0	1− G+/6− G+	2.0 V, 130 Hz, 60 μs/2.5 V, 130 Hz, 60 μs
13	39	M	5	4	187	3− G+/11− G+	2.3 V, 130 Hz, 60 μs/2.1 V, 130 Hz, 60 μs
14	59	M	4	3	250	G+ 3−/G+ 11−	2.0 V, 130 Hz, 60 μs/2.0 V, 130 Hz, 60 μs
15	41	M	14	3	100	3− G+/10− G+	3.5 V, 200 Hz, 60 μs/2.0 V, 200 Hz, 60 μs
16	55	M	9	3	0	2− G+/10− G+	2.0 V, 130 Hz, 60 μs/2.5 V, 130 Hz, 60 μs

LED L-dopa equivalent daily dose in mg

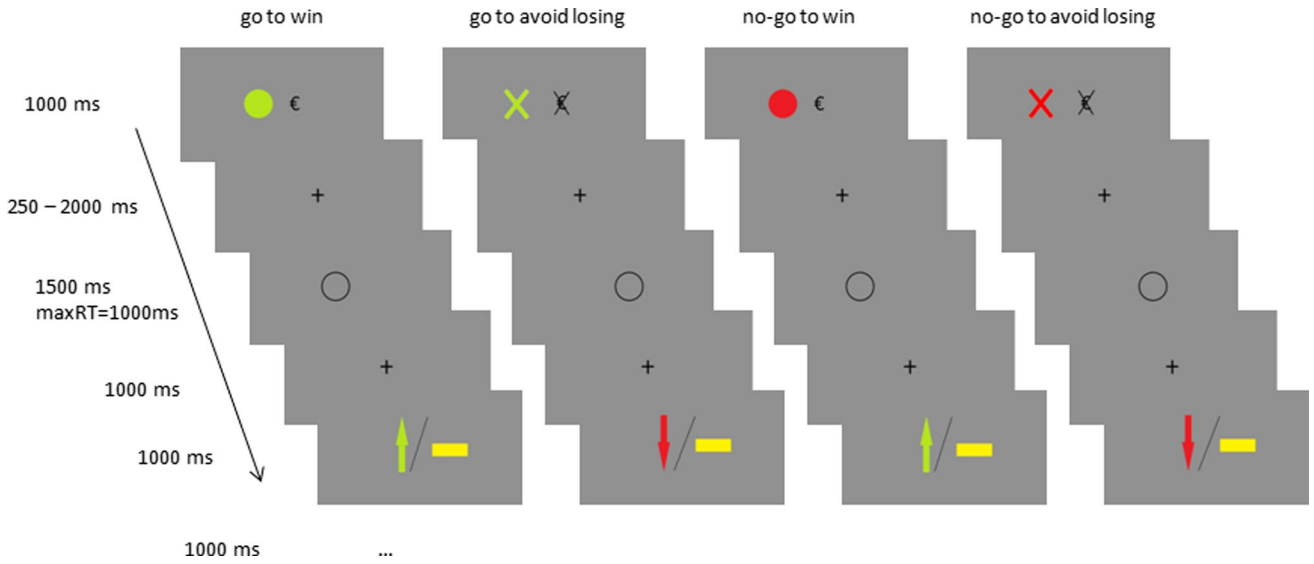

Fig. 1 Experimental design: on each trial, one of the four different cues was presented that indicated the required reaction to the coupling of action (press or do not press a button) and valence (win or lose) to a target, followed by a *black circle* appearing either on the *right or left side of a fixation cross*. In go trials, patients had to press a right or left button of a computer mouse according to the direction of the target with their preferred hand. In no-go trials, patients had to withhold a response. Feedback was given in terms of a *green upward arrow* (correct reaction, win of € 0.08), a *red downward arrow* (wrong reaction, loss of € 0.08) or a *yellow horizontal bar* (absence of win or loss) after presentation of the *black circle* and a delay of 1000 ms. 320 trials were presented in a randomized matter in four blocks of each 80 trials

Inc.). The paradigm was adapted from Guitart-Masip et al. [10] (see Fig. 1) to simplify it for patient use.

On each trial, patients first saw an iconic cue: green or red signs (O or X) combined with different € symbols (see Fig. 1). There were four trial types depending on the cues presented at the beginning of the trial: (1) "go to win": a green circle combined with a € sign indicated that a reward could be obtained by action (button press); (2) "go to avoid losing": a green cross combined with a crossed-out € sign indicated that a punishment could be avoided by action (button press); (3) "no-go to win": a red circle combined with a € sign indicated that reward could be gained by withholding an action (button press). (4) "no-go to avoid losing": a red cross combined with a crossed-out € sign indicated that a loss could be avoided by withholding action. Half of the trials (160) were go cues, the other half no-go cues.

The button press had to be made in response to a target (a black circle appearing either on the right or the left side from a fixation cross) *subsequently presented* within a time period of 250–2000 ms after the cue. Participants had to indicate the side (left or right) of the circle with a press on the corresponding mouse button within 1000 ms *with their preferred hand*. After the response, a fixation mark appeared that was followed by a feedback indicating whether the response was correct (green upward arrow) or wrong (red downward arrow) or if a punishment was avoided (yellow horizontal bar). For each correct answer, the patient won 0.08 €; for each wrong answer, 0.08 € were subtracted. The gains and losses for each trial were added to a total; at the end of the experiment, the entire amount was paid to the participant.

Experimental procedure

The experiment and the process of switching the stimulator ON or OFF were explained to the patients and confirmation of consent was affirmed. The values and response contingencies associated with each cue were fully explicit. Patients were seated in front of a computer screen, looked at a fixation cross in the middle of the screen and had to press either the left or the right button on a computer mouse with their preferred hand. During one session, 320 trials were presented in four runs with a short break (2–3 min maximum) after each 80 trials. Cues were displayed in a random manner, i.e., 80 trials were assigned to each of the four trial types ("go to win", "go to avoid losing", "no-go to win" and "no-go to avoid losing"). The randomization was carried out by Presentation.

One test session (320 trials) lasted about 40 min; the first session was preceded by a training of 15 min. In the training, patients were instructed to the functionality of the answering buttons, the cues were introduced and explained, and patients could practice the go/no-go procedure in three parts (1. presentation of and responding to the circle on either the left or right side, 2. explanation of the iconic cues and afterwards training of go/no-go trials with combined written instructions underneath the pictures, 3. training of go/no-go trials without written instructions).

The order of the ON/OFF testing was randomized across patients. Between both sessions, a break of 1 h was integrated after the DBS stimulator was switched ON or OFF, respectively, to assure a complete remission of the DBS effect. This ensured that motor symptoms had largely subsided after inducing stimulation and that the increase in motor symptoms had reasonably stabilized after terminating stimulation [12, 13]. Before the start of the second session, participants were reminded of the four different cue pictures and their outcomes.

Results

Successful trials

For the analysis of behavioral data, the percentage of successful trials (correct on time button press responses for all conditions) were analyzed (see Fig. 2). For the HC, the two-way repeated-measures ANOVA with the factors *action* (go/no-go) and *valence* (win/avoid losing) revealed a significant main effect (ME) of the factor *action* ($F(1,15) = 10.18$; $p < 0.01$) as well as a significant *action* × *valence* interaction ($F(1,15) = 4.84$; $p < 0.05$). Thus, HC performed better in no-go trials than in go trials (ME *action*) and the choice of action was modulated by the anticipation of reward; replicating former results in a version of this task in which participants were instructed on task contingencies before testing [4, 10].

For the comparison of HC and PD patients under DBS-OFF, the three-way repeated-measures ANOVA with the factors *action* (go/no-go), *valence* (win/avoid losing) and *group* (PD/HC) revealed significant main effects of the factors *action* ($F(1,15) = 9.49$; $p < 0.01$) and *group* ($F(1,15) = 6.24$; $p < 0.05$) as well as a significant *group* × *action* interaction ($F(1,15) = 6.01$; $p < 0.05$). Thus, whereas PD patients with DBS-OFF performed generally worse than HC (ME *group*), both groups performed worse in actively executing a response than in omitting one, which resulted in less successful go trials than no-go trials (ME *action*). Furthermore, this effect of action selection was stronger in PD patients under DBS OFF (*group* × *action*).

For the comparison of HC and PD patients under DBS ON, the ANOVA revealed significant main effects of the factors *action* ($F(1,15) = 8.46$; $p < 0.01$), *valence* ($F(1,15) = 5.38$; $p < 0.05$) and *group* ($F(1,15) = 5.95$; $p < 0.05$), a significant *action* × *valence*—($F(1,15) = 18.41$; $p < 0.001$), a significant *group* × *action*—($F(1,15) = 5.08$; $p < 0.05$), a significant *group* × *valence*—($F(1,15) = 8.07$; $p < 0.01$), and a significant *group* × *action* × *valence* interaction ($F(1,15) = 6.97$; $p < 0.05$). Thus, PD patients under DBS ON performed generally worse than HC (ME *group*). However, both groups performed worse in actively executing a response than in omitting one, which results in less successful go trials than no-go trials (ME *action*), and finally, both groups performed better when anticipating a reward than a loss (ME *valence*). The effects of action selection (*group* × *action*) as well as the effect of valence anticipation were stronger in PD patients with DBS ON (*group* × *valence*). Furthermore, in HC as well as PD with DBS ON the choice of action was modulated by the anticipation of reward (*action* × *valence*). Importantly, this interaction was considerably stronger in STN-DBS ON (*group* × *action* × *valence*).

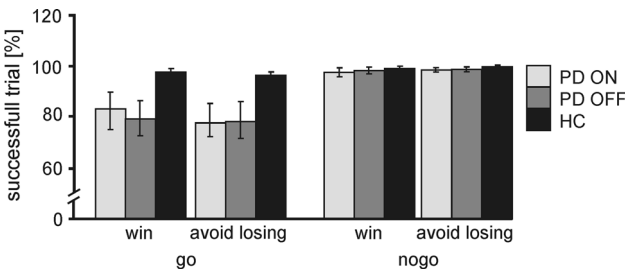

Fig. 2 The percentage of successful trials, i.e., the trials that were answered in a correct way (button presses in go trials, no responses in no-go trials), was assessed. *Light gray bars* indicate results when DBS was ON, *dark gray bars* show results when DBS was OFF, *black bars* show results of the healthy control group. All *bars* show M ± SE ***$p < 0.001$

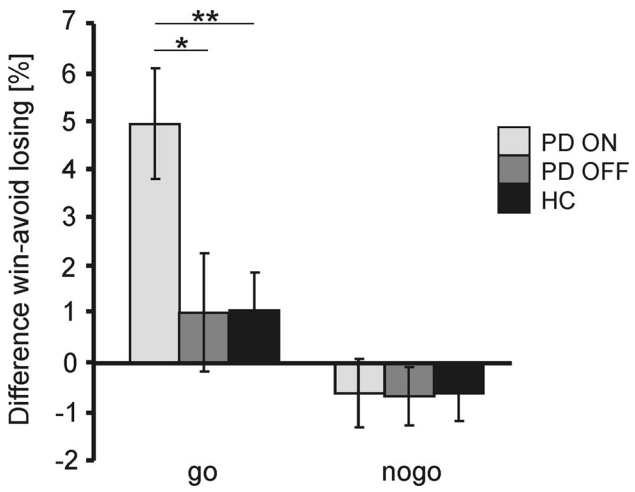

Fig. 3 For successful trials, the behavioral benefit for the reward-related gain as the difference between go to win and go to avoid losing trials (*left*) and between no-go to win and no-go to avoid losing trials (*right*) was assessed. These two scores represent the interaction between action and valence in choice accuracy (difference value of win–lose). *Light gray bars* indicate results for DBS ON, *dark gray bars* for DBS OFF and *black bars* show the difference values for healthy controls. All *bars* show M ± SE

To further elucidate the observed STN stimulation effect on the *valence* × *action* interaction—i.e., the behavioral benefit for initiating a response when anticipating a reward over the response initiation when anticipating to avoid a punishment (Pavlovian congruency effect [10])—we subsequently calculated and directly compared "*Pavlovian congruency gain indexes*" by subtracting values of avoid losing trials from win trials (see Fig. 3).

Here, PD patients under DBS ON showed the largest reward-related gain in go trials when compared to DBS OFF ($T(15) = 2.37$; $p = 0.031$) and to HC ($T(14) = 3.03$; $p = 0.008$). No differences for gain in go trials are visible between PD patients with DBS OFF and HC ($T(15) = -0.05$; $p = 0.96$). For no-go trials, no differences were observed between all three groups (DBS ON vs. DBS OFF: $T(15) = 0.12$; $p = 0.91$; DBS ON vs. HC: $T(15) = 0.0$; $p = 1.0$); DBS OFF vs. HC: $T(15) = -0.09$; $p = 0.93$). Subsequently, the patientś differential parameters were correlated with the individual daily L-dopa equivalent dose (in mg). Neither under DBS ON ($r = .29$, $p = 0.27$) nor in the OFF condition ($r = -0.03$, $p = 0.91$), the Pavlovian congruency effect (i.e., the benefit for initiating a response when anticipating a reward over the response initiation when anticipating to avoid a punishment) was modulated by the dopaminergic medication.

Reaction times

For the comparison of RT in the go trials between HC and PD patients under DBS ON and OFF, the separate ANOVAs with the factors *valence* (win/avoid losing) and *group* (PD patients ON or OFF/HC) revealed a significant main effects for the factor *group* only (HC/PD ON ($F(1,15) = 10.36$; $p = 0.006$);—HC/PD OFF ($F(1,15) = 14.89$; $p = 0.002$). HC were faster compared to PD patients when DBS was ON (go to win: $T(14) = 3.33$; $p = 0.005$; go to avoid losing: $T(14) = 2.79$; $p = 0.014$) and OFF (go to win: $T(14) = 3.52$; $p = 0.003$); go to avoid losing: $T(14) = 3.65$; $p = 0.002$). Neither HC nor PD differed in their RT for go to win versus go to avoid losing trials HC: ($T(15) = -1.42$; $p = 0.18$), PD ON: ($T(15) = -0.56$; $p = 0.59$), PD OFF: ($T(15) = -0.76$; $p = 0.46$).

Discussion

As in a previous study with healthy old adults [14], our HC took advantage of a Pavlovian congruency between action and reward; they showed a behavioral benefit for initiating a response when anticipating a reward over the response initiation when anticipating to avoid a punishment. PD patients with DBS OFF were overall slower and less accurate independent of valence. Also, the Pavlovian congruency effect observed in HC did not reach significance in PD DBS OFF, presumably because there was high performance variability (Fig. 3). Importantly, DBS modulation of the STN enhanced the interaction of action and valence anticipation such that it was considerably stronger than under DBS OFF and in HC. PD patients under DBS ON showed the largest reward-related gain in go trials when compared to DBS OFF and to HC.

Thus, our present data show that STN-DBS does not lead to a valence-independent motor improvement. Instead, our data demonstrate the impact of STN-DBS on motivational action control in PD. We hypothesize that this DBS-related enhancement of the interaction between action and valence (Pavlovian congruency) results from a modulation of both the limbic ventral as well as the motor dorsal striatum.

Previous studies investigating the effects of STN-DBS on the motor domain in PD reported impairments of the ability to withhold strong predominant answers in response conflict tasks as the Stroop Task [15], the Simon reaction task [16], go/no-go tasks [2, 17] and decision-making tasks [8]. Our task also involved a response conflict component because participants had to sometimes make actions and sometimes withhold actions to obtain a reward or to avoid punishment. Thus, a strategy to always act for a reward or to avoid punishment would have impaired performance. The selective effect of STN-DBS on the go-reward condition rules out a general increase in response impulsivity. This is remarkable because STN-DBS acts via a reduction of the inhibitory influence of the BG nuclei on thalamocortical projections in the indirect BG-pathway [1] and it is feasible to assume STN-DBS could lead to a general motor improvement irrespective of an expected reward. As for limbic consequences, STN-DBS has been shown to influence mood states such as depression, mania, anxiety or apathy [18], as well as to alter emotion processing by either improving [19] or worsening emotion recognition [20], and finally is also affecting aversive and appetitive motivational processing [21]. It is, therefore, feasible to assume that a combination of limbic and motor consequences of DBS led to the behavioral pattern that we have observed here. Indeed, there is evidence indicating a role of the STN in reward and valence coding [22–24].

A limitation of our study is that patients were tested while they remained on their supplementary dopaminergic medication in conjunction with DBS. Thus, this study was not designed to isolate the effect of PD per se on the interaction between action and valence. Therefore, it is likely that our results underestimate the impact of the disease on this interaction. Furthermore, by the same argument, our results might overestimate the impact of STN-DBS on the reported action and valence interaction due to possible amplifying effects of the dopaminergic medication.

In conclusion, we show that STN-DBS in PD invigorates actions specifically when these actions lead to rewards. There is no enhancement of actions that are performed to avoid punishment. This tight coupling between action and valence indicates that STN-DBS influences the congruency between action and valence (Pavlovian congruency) rather than enhancing action initiation per se.

Acknowledgments This work was funded by DFG-SFB 779/TPA 2 (T.Z., H.-J.H. and ED), TPA 3 (H.-J.H.) TPA 7 (ED) and TP A11 (J.V. and H.-J.H.), and DFG He 1531/11-1 (J.V. and H.-J.H.).

Conflicts of interest CW & TZ report no disclosure. IG received honoraria for speaking from GlaxoSmithKline, TEVA pharma, Medronic and St. Jude Medical. JV is member of the Medtronic Inc. advisory board and receives occasionally honoraria. MGM reports no disclosure. HJH reports no disclosure. ED reports no disclosure.

Ethical standard This study has been approved by the local ethics committee (University of Magdeburg, Germany) and has been performed in accordance with the ethical standards of the 1964 Declaration of Helsinki.

References

1. Limousin P, Krack P, Pollak P, Benazzouz A, Ardouin C, Hoffmann D, Benabid AL (1998) Electrical stimulation of the subthalamic nucleus in advanced Parkinson' disease. N Eng J Med 339:1105–1111
2. Ballanger B, van Eimeren T, Moro E, Lozano AM, Hamani C, Boulinguez P, Pellecchia G, Houle S, Poon YY, Lang AE, Strafella AP (2009) Stimulation of the subthalamic nucleus and impulsivity: release your horses. Ann Neurol 66:817–824
3. Guitart-Masip M, Economides M, Huys QJ, Frank MJ, Chowdhury R, Duzel E, Dayan P, Dolan RJ (2014) Differential, but not opponent, effects of L-DOPA and citalopram on action learning with reward and punishment. Psychopharmacology 231:955–966
4. Guitart-Masip M, Huys QJM, Fuentemilla L, Dayan P, Duzel E, Dolan RJ (2012) Go and no-go learning in reward and punishment: interactions between affect and effect. NeuroImage 62:154–166
5. Frank MJ, Seeberger LC, O'Reilly RC (2004) By carrot or by stick: cognitive reinforcement learning in parkinsonism. Science 306:1940–1943
6. Salamone JD, Correa M, Mingote SM, Weber SM (2005) Beyond the reward hypothesis: alternative functions of nucleus accumbens dopamine. Curr Opin Pharmacol 5:34–41
7. Berridge KC, Robinson TE (1998) What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res Rev 28:309–369
8. Frank MJ (2006) Hold your horses: a dynamic computational role for the subthalamic nucleus in decision making. Neural Netw 19:1120–1136
9. Fleming SM, Thomas CL, Dolan RJ (2010) Overcoming status quo bias in the human brain. PNAS 107:6005–6009
10. Guitart-Masip M, Fuentemilla L, Bach DR, Huys QJM, Dayan P, Dolan RJ, Duzel E (2011) Action dominates valence in anticipatory representations in the human striatum and dopaminergic midbrain. J Neurosci 31:7867–7875
11. Elias WJ, Fu KM, Frysinger RC (2007) Cortical and subcortical brain shift during stereotactic procedures. J Neurosurg 107:983–988
12. Hristova A, Lyons K, Tröster AI, Pahwa R, Wilkinson SB, Koller WC (2000) Effect and time course of deep brain stimulation of the globus pallidus and subthalamus on motor features of Parkinson's disease. Clin Neuropharmacol 23:208–211
13. Lopiano L, Torre E, Benedetti F, Bergamasco B, Perozzo P, Pollo A, Rizzone M, Tavella A, Lanotte M (2003) Temporal changes in movement time during the switch of the stimulators in Parkinson's disease patients treated by subthalamic nucleus stimulation. Eur Neurol 50:94–99
14. Chowdhury R, Guitart-Masip M, Lambert C, Dolan R, Duzel E (2013) Structural integrity of the substantia nigra and subthalamic nucleus determines the flexibility of instrumental learning in old age. Neurobiol Aging 34:2261–2270
15. Schroeder U, Kuehler A, Haslinger B, Erhard P, Fogel W, Tronnier VM, Lange KW, Boecker H, Ceballos-Baumann AO (2002) Subthalamic nucleus stimulation affects striato-anterior cingulate cortex circuit in a response conflict task: a PET study. Brain 125:1995–2004
16. Wylie SA, Ridderinkhof KR, Elias WJ, Frysinger RC, Bashore TR, Downs KE, van Wouwe NC, van den Wildenberg WP (2010) Subthalamic nucleus stimulation influences expression and suppression of impulsive behavior in Parkinson's disease. Brain 133:3611–3624
17. Hershey T, Revilla FJ, Wernle A, Gibson PS, Dowling JL, Perlmutter JS (2004) Stimulation of STN impairs aspects of cognitive control in PD. Neurology 62:1110–1114
18. Temel Y, Kessels A, Tan S, Topdag A, Boon P, Visser-Vandewalle V (2006) Behavioural changes after bilateral subthalamic stimulation in advanced Parkinson disease: a systematic review. Parkinsonism Relat Disord 12:265–272
19. Castner JE, Copland DA, Silburn PA, Coyne TJ, Sinclair F, Chenery HJ (2007) Lexical-semantic inhibitory mechanisms in Parkinson's disease as a function of subthalamic stimulation. Neuropsychologia 45:3167–3177
20. Schroeder U, Kuehler A, Hennenlotter A, Haslinger B, Tronnier VM, Krause M, Pfister R, Sprengelmeyer R, Lange KW, Ceballos-Baumann AO (2004) Facial expression recognition and subthalamic nucleus stimulation. J Neurol Neurosurg Psychiatry 75:648–650
21. Serranová T, Sieger T, Dušek P, Růžička F, Urgošík D, Růžička E, Valls-Solé J, Jech R (2013) Sex, food and threat: startling changes after subthalamic stimulation in Parkinson's disease. Brain 6:740–745
22. Lardeux S, Pernaud R, Paleressompoulle D, Baunez C (2009) Beyond the reward pathway: coding reward magnitude and error in the rat subthalamic nucleus. J Neurophysiol 102:2526–2537
23. Lardeux S, Paleressompoulle D, Pernaud R, Cador M, Baunez C (2013) Different populations of subthalamic neurons encode cocaine versus sucrose reward and predict future error. J Neurophysiol 100:1497–1510
24. Baunez C, Dias C, Cador M, Amalric M (2005) The subthalamic nucleus exerts opposite control on cocaine and 'natural' rewards. Nat Neurosci 8:484–489