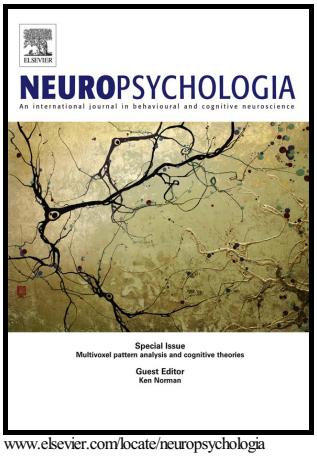

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IN PARKINSON'S DISEASE STN STIMULATION ENHANCES RESPONSIVENESS OF MOVEMENT INITIATION SPEED TO HIGH REWARD VALUE

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Abstract

Objective

The subthalamic nucleus (STN) is part of the motor, associative, and limbic cortico-striatal circuits through which it can influence a range of behaviours, with preclinical and clinical evidence suggesting that the STN is involved in motivational modulation of behaviour. In the present study, we investigated if in Parkinson's disease (PD) motivational modulation of movement speed is altered by deep brain stimulation (DBS) of the STN (STN-DBS).

Methods

We studied the effect of monetary incentive on speed of movement initiation and execution in a computer-based simple reaction time task in 10 operated patients with Parkinson's disease using a STN DBS ON/OFF design and also in 11 healthy participants.

Results

Prospect of reward improved speed of movement initiation in PD patients both with STN-DBS on and off. However, only with STN-DBS ON, the patients showed greater speeding of initiation time with

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higher reward magnitude, suggesting enhanced responsivity to higher reward value. Also, on the rewarded trials, PD patients ON stimulation made more anticipation errors than on unrewarded trials, reflecting a propensity to impulsive responses triggered by prospect of reward by subthalamic stimulation. The motivational modulation of movement speed was preserved and enhanced in PD with STN-DBS.

Conclusion

Motivational modulation of movement speed in PD is maintained with STN-DBS, with STN stimulation having a further energizing effect on movement initiation in response to greater incentive value. Our results suggest that STN plays a role in integrating motivational influences into motor action, which may explain some previous reports of STN-DBS induced impulsivity with increased motivational salience of stimuli.

KEYWORDS: Parkinson's disease; deep brain stimulation; subthalamic nucleus; motivation; reaction times; reward

1. INTRODUCTION

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective treatment for motor symptoms of advanced Parkinson's disease (PD) (Williams, et al., 2010). STN DBS may improve various aspects of non-motor symptoms, such as pain, sleep problems and autonomic dysfunction (Cury, et al., 2014; Kim, Jeon, & Paek, 2015) and does not produce any major deficits in global cognition (Parsons, Rogers, Braaten, Woods, & Troster, 2006) . Together with the striatum, the STN is one of the input areas of the basal ganglia and features in the classical loops linking the basal ganglia to cortical areas, with motor, associative, and limbic circuits distinguished(Alexander, DeLong, & Strick, 1986). As an integral part of the hyperdirect and indirect pathways, the STN is well-placed to influence a range of behaviours, although evidence for the effect of STN DBS on motivational aspects of behaviour has been so far conflicting. It has been reported that STN stimulation induces or worsens apathy (Gervais-Bernard, et al., 2009; Krack, et al., 2003; Saint-Cyr, Trepanier, Kumar, Lozano, & Lang, 2000), while others found no effect or even improvement of apathy following STN

DBS surgery (Castelli, et al., 2007; Czernecki, et al., 2005; Schuepbach, et al., 2013). Similarly, STN DBS has been linked with post-surgical de novo emergence of pathological gambling or shopping, but also with improvement of impulse control disorders (Amami, et al., 2015; Demetriades, Rickards, & Cavanna, 2011; Lim, et al., 2009; Moum, et al., 2012). These side-effects have been partly explained by diffusion of current to associative and limbic subthalamic territories, although there is still a debate concerning the impact of STN DBS per se on motivational processes, as opposed to this effect being the result of drug modifications following surgery (Pagonabarraga, Kulisevsky, Strafella, & Krack, 2015)

Together with the motor and associative sections, the STN also has a limbic territory, verified by imaging in humans (Lambert, et al., 2012) and preclinical and clinical studies suggest that the STN is indeed involved in modulating motivational processes. STN lesions and DBS in experimental studies on rats increase motivation for food, but show an opposite effect for cocaine (Baunez & Robbins, 1997). Increased sensitivity to food reward was also found in PD patients with STN DBS and was associated with weight gain following surgery (Serranova, et al., 2011) . High-frequency STN DBS has been reported to improve reward-based decision-learning in PD (van Wouwe, et al., 2011) . Conversely, STN DBS transiently enhanced loss-chasing behaviour on a gambling task (Rogers, et al., 2011) and increased risky choices on the Iowa Gambling task (IGT) in PD in some studies (Evens, et al., 2015; Oyama, et al., 2011), but no such effect on the IGT was observed by others (Czernecki, et al., 2005; Lule, et al., 2012). These apparently opposite effects of STN DBS/lesioning on different aspects of motivational influence on behaviour and the mechanisms through which they might be occurring remain under-investigated.

One aspect of motivational influence on behaviour that may be clinically relevant for PD patients is motivational modulation of movement speed. This is an intrinsic property of the motor system that allows individuals to react and move faster than their usual limits in situations with appropriate motivational contexts or stimuli. Notably, such motivational modulation of movement speed is preserved in patients with PD and may help them overcome bradykinesia in particular situations. This phenomenon is epitomised by examples of extreme life situations such as a fire that provoke “paradoxical kinesis” (Glickstein & Stein, 1991), a speeding up of normally bradykinetic movements in PD, which has also been studied and demonstrated experimentally in these patients (Griffin, et al., 2011; Kojovic, et al., 2014; McDonald, et al., 2015; Shiner, et al., 2012). It is thus

reasonable to propose that enhanced motivation would also positively influence movement speed of PD patients in common real-life situations, thus helping them to temporarily counteract slowness. Given that STN-DBS has become the surgical procedure of choice in advanced PD, and in light of the proposed role of the STN in motivational behaviour, we were interested to investigate if motivational modulation of movement speed in PD would be altered by STN-DBS.

2. METHODS

2.1. Participants

We assessed 10 (9 men, mean age 58 years, range: 39-78 years) patients with Idiopathic Parkinson's disease (IPD) who underwent bilateral Deep Brain Stimulation (DBS) surgery of the Subthalamic Nucleus (STN) in the Functional Neurosurgery Unit at the National Hospital for Neurology and Neurosurgery , London, UK. All patients were operated at least six months prior to entering the study and had post-surgical MRI evidence of correct positioning of at least one of the electrode contacts in or near the sensorimotor section of the STN. All patients had substantial improvement of clinical symptoms post-surgery. The clinical and demographic characteristics of the patients and the stimulation parameters are given in Table 1. Eleven aged-matched healthy participants, with no history of neurological, s physical or psychiatric illness, and no history or head injury, alcohol or drug abuse served as controls. According to the Edinburgh Handedness Inventory all participants were strongly right-handed. The study was approved by the local ethics committee, and written informed consent was obtained from all participants.

2.2. Experimental design

The effect of reward on motor performance was assessed with a computer-based Simple Reaction Time (SRT) task. PD patients were studied in 2 different sessions separated by at least 1 week, ON and OFF stimulation. The order of ON and OFF sessions was counterbalanced, with five patients being tested first in OFF and five first in the ON DBS state. Patients were always studied after overnight withdrawal of medications. To control for potential practice and fatigue effects, the healthy controls also completed the task twice. All participants completed a number of additional measures of cognition, mood and personality.

2.2.1. Experimental Task: Warned and unwarned Simple Reaction time (SRT)

We used the warned and unwarned simple RT task (Supplementary Figure) as in our previous study (Kojovic, et al., 2014). In brief, stimuli were presented on a computer screen and responses were made with the index finger of the right hand on a response box with two buttons: a home key and a response key. In each session, participants completed 4 blocks of 100 trials, each block consisting of 50 warned simple reaction time (wSRT) and 50 unwarned simple reaction time (uSRT) trials, randomly mixed. On pressing the home key a fixation cross appeared on the screen. On unwarned trials (uSRT), the fixation cross was followed, after a variable delay of 1-4s, by a filled square representing imperative signal , when participants were required to release the home key and move to and press the response key, as quickly as possible. On warned trials (wSRT), the fixation cross was replaced, after a variable delay of 1-4s , by an empty square representing a warning signal. 1600ms later this square was filled to become solid white, and this constituted the imperative signal. For wSRT trials, participants were instructed to make use of the warning signal, to prepare to respond to presentation of the imperative signal. This kind of warned trial requires the participant to hold/inhibit his response and release it on presentation of the imperative stimulus. Participants were thus instructed to wait for the presentation of the imperative stimulus, to discourage anticipatory responses.

2.2.2. Measurement of initiation times, movement times and errors

The time from presentation of the imperative stimulus to the release of the 'home' key was measured as the initiation time (IT). The time from release of the 'home' key to pressing the 'response' key was measured as the movement time (MT). Both IT and MT were recorded by the computer to the nearest millisecond. Two types of error were recorded: anticipation errors (IT less than or equal to 100 ms) and long responses (IT greater than 2000 ms). Trials with error data were excluded and replaced with a new trial.

2.2.3. Provision of monetary incentive for speeding up reaction times

Each session was organised in the same order, starting with 2 unrewarded and followed by 2 rewarded blocks, imposed by the need to establish a baseline RT for each participant before introduction of monetary incentive. First two blocks were performed without financial incentive, with any changes in IT and MT from the first to the second block providing a measure of change as a result

of practice/task repetition. Participants were not told in advance that they would receive any reward in future blocks. At the end of the second block, participants were provided with feedback of their reaction time in the previous block and were instructed that for every 10 ms they speeded their reaction time in the third block, they would receive a monetary reward of 50 pence. At the end of the third block, they were again given feedback on their performance and the amount of money gained was displayed on the screen. Prior to the fourth block, participants were instructed that they would receive a monetary reward of 100 pence for every 5 ms they improved their reaction times in the following block. The monetary incentive was real and the participants were provided with the money gained at the end of the study.

2.3. Clinical and other measures

The severity of the motor symptoms in PD patients was assessed with the motor section of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (Goetz, et al., 2008) (Table 1). To screen for depression, apathy and cognitive impairment, we used the Beck Depression Inventory (BDI) (Beck & Beamesderfer, 1974), the Marin Apathy Scale (MAS) (Marin, Biedrzycki, & Firinciogullari, 1991) and the Mini Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) respectively (Table 1).

2.4. Statistical analysis

T- tests were used to compare demographic differences or differences on assessment scales between patients and healthy participants. The effect of monetary incentive on initiation time (IT) and movement time (MT) was analysed separately. To assess the effect of DBS stimulation on reward responsiveness we compared PD patients ON and OFF stimulation in a repeated measures ANOVAs (RMANOVA) with STIMULATION (2 levels: DBS ON and DBS OFF), TASK (2 levels: uSRT and wSRT) and BLOCK (4 levels), as within-subject factors. When there was an effect of reward in the primary analysis, to determine if modulation of IT or MT by the magnitude of the monetary incentive was influenced by STN DBS, data from the two unrewarded blocks were averaged and data from the rewarded blocks 3 (reward 50p) and 4 (reward 100p) were expressed as a percentage of improvement

relative to the unrewarded blocks and a RMANOVA with factors STIMULATION, TASK and REWARD MAGNITUDE (50 p vs 100p) was conducted.

For healthy participants, we first ensured that performance did not differ across the two sessions, by conducting a RMANOVA with factors SESSION (2 levels), TASK (2 levels) and BLOCK (4 levels) and then collapsed the control data across the two sessions for subsequent analyses. As a secondary analysis, we assessed how measures of movement speed (IT and MT) compared between PD patients and healthy participants: data from PD patients with DBS ON and OFF were separately compared to averaged data from healthy participants in ANOVAs with a factor GROUP (PD OFF vs. healthy participants or PD ON vs. healthy participants) as a between-subject factor, and factors TASK and BLOCK as within-subject factors. Post-hoc Tukey tests with corrections for multiple comparisons were used to further analyse significant main effects or interactions.

The number of anticipation errors and long responses across blocks in PD patients and healthy participants were not normally distributed and therefore non-parametric tests were used for the analysis. Differences in anticipation errors and long responses in PD patients OFF and ON DBS were analysed with the Wilcoxon signed ranked test . For assessing differences between PD patients and healthy participants Mann-Whitney U tests were used . As a secondary analysis , we used a Friedmann ANOVA to asses the difference in errors between rewarded (averaged number of errors in blocks 3 and 4) and unrewarded blocks (averaged number of errors in blocks 1 and 2).

The associations between demographic data, clinical data and performance on the reaction time task were examined with Pearson correlation. The results are presented as mean values ± 1 standard error (SE) or as median with a range, depending on the distribution of the data.

3. RESULTS

There was no difference in demographic characteristics between PD patients and healthy participants. PD patients scored worse than healthy participants on the MAS scale (p=0.01), while no difference was found on the Beck depression inventory or MMSE (Table 2). As expected, PD patients had lower total motor UPDRS in the DBS ON than DBS OFF state (t=5.7; p< 0.001).

3.1. Effects of STN DBS OFF vs ON for PD patients

The detailed results of the analysis are given in the supplementary table.

3.1.2. Initiation time

RMANOVA revealed that the main effect of STIMULATION was significant ($F(1, 9) = 4.85$; $p=0.05$) due to faster IT with DBS ON than OFF. The main effect of TASK ($F(1, 9) = 40.5$; $p<0.001$) was also significant, because IT was faster in the presence of the warning signal (wSRT vs uSRT). The main effect of BLOCK was also significant ($F(3, 27) = 5.14$; $p=0.006$), due to faster IT in rewarded block 3 than in unrewarded block 2 ($p=0.03$) and in rewarded block 4 than in unrewarded block 2 ($p=0.01$). All the 2-way and 3-way interactions were not significant, indicating that although PD patients had overall faster IT WITH DBS ON than OFF, the reward responsiveness, that is speeding of IT with prospect of reward in blocks 3 and 4 relative to the unrewarded block 2, was preserved irrespective of stimulation condition (Figure 1).

To further determine if modulation of IT by the magnitude of the monetary incentive was influenced by STN-DBS, RMANOVA with factors STIMULATION, TASK and REWARD MAGNITUDE (50 p vs 100p) was conducted (see section 2.4.). This analysis revealed a significant STIMULATION x REWARD MAGNITUDE interaction ($F(1, 9) = 6.83$; $p=0.03$), due to greater improvement/speeding of IT with higher reward (100p) in the DBS ON relative to the DBS OFF condition ($p=0.02$), thus indicating that STN stimulation induced differentially greater responsiveness to higher reward value and greater improvement of IT in anticipation of such higher reward (Figure 2).

3.1.2. Movement time

For PD patients, RMANOVA revealed a significant main effect of STIMULATION ($F(1, 9) = 38.2$; $p<0.001$), due to overall faster MT with DBS ON than OFF. There was also a significant effect of BLOCK ($F(3, 27) = 4.05$; $p=0.02$), which was due to longer MT in block 2 vs block 1 ($p=0.01$); while no other differences between blocks was found. The main effect of TASK was not significant. The 2-way STIMULATION x BLOCK interaction was also significant $F(3, 27) = 6.06$; $p=0.002$), but post hoc analysis revealed that this was due to shorter MTs with DBS ON stimulation than with DBS OFF in all 4 blocks ($p<0.001$) (Figure 3). The other main effects or interactions were not significant. These results indicate that there was no effect of reward on MT with DBS ON or OFF (Figure 3).

3.2. Comparison of patients and healthy controls

The performance of the healthy participants did not differ across the two sessions. RMANOVA revealed that the main effect of SESSION was not significant for either IT ($F(1, 10) = 0.66$; $p=0.45$) or MT ($F(1, 10) = 0.46$; $p=0.51$). Neither 2- or 3-way interactions were significant. This excluded the possibility of practice and fatigue effects occurring as a result of completing the task twice. We therefore collapsed the control data across the two sessions for subsequent analyses.

3.2.1. Initiation time

We compared the patients' data ON stimulation with that of healthy participants. An ANOVA revealed significant main effects of GROUP ($F(1, 19) = 19.2$; $p<0.001$) due to faster IT for healthy participants, significant main effects of TASK ($F(1, 19) = 101$; $p<0.001$) due to faster IT in the warned SRT task, and BLOCK ($F(3, 57) = 10.6$; $p<0.001$), which was due to faster IT in rewarded block 4 vs unrewarded block 1 ($p=0.0002$) and rewarded blocks 3 and 4 compared to unrewarded block 2 ($p=0.03$ and $p=0.001$, respectively) according to post-hoc analysis. The GROUP X BLOCK interaction was also significant ($p=0.01$), with post-hoc analysis showing that this was due to faster IT for healthy participants than patients with STN DBS on in all 4 blocks ($p<0.001$ for all blocks) .

For patients' performance DBS OFF versus healthy participants, the analogous ANOVA demonstrated the main effect of GROUP was significant ($F(1, 19) = 44.9$; $p<0.001$), due to faster IT for healthy participants. The main effect of TASK was also significant ($F(1, 19) = 83.7$; $p<0.001$), because IT was faster in wSRT compared to uSRT. The main effect of BLOCK was also significant ($F(3, 57) = 6.55$; $p<0.001$) due to shorter IT in rewarded block 3 vs unrewarded block 1 ($p=0.01$) and rewarded blocks 3 and 4 compared to unrewarded block 2 ($p=0.0003$ and $p=0.02$, respectively). There were no significant interactions. These results indicate that PD patients with both STN-DBS ON and OFF were slower than healthy participants, but improved IT to the similar extent in response to reward.

To determine if there was a difference in modulation of initiation time by the reward magnitude between PD patients and healthy participants , we conducted an ANOVA with GROUP (PD STN DBS ON vs. healthy participants or PD STN DBS OFF vs healthy participants) as a between- subjects factor and TASK and REWARD MAGNITUDE as within-subjects factors. When comparing PD patients with STN DBS ON to healthy participant, the analysis revealed a significant effect of REWARD MAGNITUDE ($F(1, 9) = 5.05$; $p=0.03$), due to greater speeding of IT with higher reward (100p). Other main factors or interactions were not significant. This result indicates that PD patients

with STN DBS ON behaved the same as healthy participants in response to higher monetary incentive, by speeding up ITs. Comparing PD patients with STN DBS OFF to healthy participants revealed no significant effect of any of the main factors or their interactions.

3.2.2. Movement time (Figure 4, Supplemental Table)

Healthy participants had faster MTs than patients in all blocks (Figure 3) irrespective of the patients' stimulation condition (PD DBS ON vs. Healthy Participants $F(1,19)= 14.5$; $p<0.001$, PD DBS OFF vs. Healthy Participants 14.5 $F(1,19)= 54$; $p<0.001$). There was no difference in the effect of reward on MTs between patients with STN DBS ON or OFF and healthy participants, as indicated by the absence of any significant interactions between the factors.

3.3. Errors: anticipation errors and long responses

The median number of AE and LR errors across blocks are presented in Table 3. Across all blocks, no overall difference in AEs for PD patients ON vs. OFF stimulation was found, either in the uSRT ($p=0.07$) or wSRT task ($p= 0.9$). However, on the wSRT task, PD patients ON stimulation made more AE errors on the rewarded than on the unrewarded blocks ($z= -2.0;p=0.04$) (Figure 4), while this was not observed with DBS OFF ($z=-1.4;p=0.2$). PD patients with DBS OFF made overall more AEs than healthy participants in the wSRT task ($z=-3.12;p=0. 003$). By contrast, the PD patients ON stimulation did not differ in AEs from healthy participants in either of the SRT tasks ($p=0.5$ for uSRT, $p=0.56$ for wSRT). There was no correlation between the number of AEs in the rewarded blocks and the improvement of either IT or MT with reward expectancy.

There was no difference between DBS ON and OFF in the number of long responses, irrespective of task or presence/absence of reward. Irrespective of stimulation condition, patients had more long responses than healthy participants (PD On vs HC, $z=-2.6$; $p=0.02$; PD OFF vs HC, $z=-2.6$, $p=0.02$).

3.4. Correlations

The patients' age, disease duration, severity of motor symptoms on the UPDRS, scores on the BDI, MAS, or MMSE did not have any noteworthy correlations with reward responsiveness on the reaction time task.

4. DISCUSSION

The present study of PD patients with bilateral STN-DBS revealed that the prospect of reward improved speed of movement initiation irrespective of whether the stimulators were ON or OFF and despite the elevated levels of self-reported apathy for the patients relative to the healthy controls. Importantly, the patients with DBS ON showed greater responsivity to higher reward value than with DBS OFF. PD patients ON stimulation made more anticipation errors on the rewarded than on unrewarded trials of the warned SRT, suggesting a propensity for STN stimulation to induce impulsive premature responses with the prospect of reward.

Our results are conistent with the functional models of basal ganglia. Within the BG model featuring the direct , indirect and hyperdirect pathways (Albin, Young, & Penney, 1989, 1995; M. R. DeLong, 1990) , the STN is a relay nucleus of the indirect pathway as well as receiving direct cortical input via the hyperdirect pathway. The indirect pathway is considered a “no go” pathway that inhibits movements via the motor circuit, but may also inhibit thoughts, emotions and motivational behaviour through the associative and limbic BG circuits, as the intrinsic organisation and processing of information is considered to be the same in all parallel BG circuits (M. DeLong & Wichmann, 2010). Stimulating the STN may disinhibit the limbic circuits analogous to the disinhibition of motor circuits, resulting in increased motivational modulation of speed of movement initiation that we have observed. However, it remains unclear how the STN translates motivational incentive to behavioural output. The subthalamic area may be a part of the functional system where integration of limbic and motor aspects of behaviour occur (Mallet, et al., 2007), or it may have a role in the translation of already integrated activities into behavioural performance (Sauleau, Eusebio, Vandenberghe, Nuttin, & Brown, 2009).

One interpretation of our finding of different effect of reward magnitude on initiation time in the STN DBS ON vs. OFF condition may be that it could be reflecting the resistance to fatigue in the STN-DBS ON state. However, we argue that improvement of initiation time in the block with the higher reward, that was selectively present in the DBS ON condition, represents a genuine effect of stimulation. First, we did not observe such an effect of higher reward in our previous study in advanced PD patients tested “on” dopaminergic medication. In medicated PD patients, reward magnitude had no significant effect on speeding up of initiation time either “on” or “off” medication (Kojovic, et al., 2014) . Second, previous studies on the effect of STN DBS on fatigue in PD patients showed that STN DBS does not improve fatigue or may even trigger fatigue in a proportion of patients

after stimulation (Chou, Persad, & Patil, 2012). Fatigue is a common non-motor symptom following DBS surgery (Kluger, et al., 2012) and may be an important side effect of long-term stimulation, as the level of fatigue was found to increase during follow-up periods of up to 9 years after surgery (Lilleeng, Gjerstad, Baardsen, Dalen, & Larsen, 2015). Therefore, it is unlikely that in the present study PD patients were selectively resistant to fatigue in the STN DBS ON condition, allowing them to further speed-up their initiation time in the higher reward value condition. Finally, the effect of reward magnitude in the STN DBS ON condition was found only for the initiation time and not the movement time, also suggesting the specificity of the reward effect.

We found that with STN stimulation, patients made more anticipation errors in the rewarded compared to the unrewarded blocks of the warned SRT task, indicating that patients were less able to keep premature responses in check when STN DBS was ON, on trials when expecting monetary incentive as a reward for speeding up of IT. This is in agreement with animal studies suggesting that STN lesions may heighten incentive motivation for food and improve RTs, however in association with increasing of premature responding (Baunez, Nieoullon, & Amalric, 1995; Uslaner & Robinson, 2006). An increasing body of evidence based on STN DBS on vs. off methodology also suggests that STN DBS in PD patients is associated with a deficit in inhibitory control over proponent responses (Jahanshahi, 2013; Jahanshahi, Obeso, Rothwell, & Obeso, 2015). The STN receives direct cortical information through the “hyperdirect pathway” (Monakow, Akert, & Kunzle, 1978; Nambu, Tokuno, & Takada, 2002), which is then relayed to the basal ganglia output structures. In Frank ‘s computational model (Frank, 2006) , the role of STN is to issue a global “no go” signal via its excitatory projections to the pallidum, to allow time for accumulation of information and reflection during decision-making, to prevent premature and impulsive responding. Accordingly, on a probabilistic decision-making task, the disruption of STN activity when STN DBS was ON was associated with faster reaction times of PD patients and failure to slow down when faced with the decision-conflict of choosing between two stimuli with high reward value (Frank, Samanta, Moustafa, & Sherman, 2007). In contrast to such impulsive action induced by STN DBS, when the STN stimulators were OFF , patients had slower reaction times in these high conflict trials, similar to non-operated PD patients and healthy controls. Similarly, in the present study, the prospect of reward was associated with the speeding of IT, which was significantly greater with higher reward value with STN DBS ON. The observed sensitivity to reward magnitude in our patients with STN DBS ON is consistent with animal studies, showing that

neuronal activity in the STN may be differentially modulated in relation to reward value (Lardeux, Pernaud, Paleressompoulle, & Baunez, 2009).

Nevertheless, it should be noted that the overall number of AEs in our study was small (Figure 4) and there were patients who improved their IT without increased AEs and there was no correlation between AEs and speeding of IT with monetary reward. This suggests that the enhancement of motivational modulation of movement speed by STN DBS was not simply mediated by increased impulsivity. The direction of effect may in fact be the reverse. The enhanced motivational modulation of movement initiation induced by STN DBS could have resulted in impulsivity and premature responding. However, this hypothesis remains to be proven on a larger sample of patients and preferably using a task with a more powerful motivational incentive.

Our patients were studied after overnight withdrawal of dopaminergic treatment, in order to isolate the effect STN DBS per se, independently from the effects of dopaminergic therapy on the motivational modulation of movement speed. Dopaminergic therapy enhances physical effort in response to reward (Chong, et al., 2015), suggesting that motivational factors may have a greater effect on movement vigour when patients are ‘‘on’’ medication. In our previous study on medically treated PD patients, we found that although the prospect of reward improved initiation times to a similar extent both ‘‘off’’ and ‘‘on’’ dopaminergic medication, patients made fewer AEs when tested “on” medication (Kojovic, et al., 2014), opposite to the effect of STN DBS observed in the present study. Thus, “paradoxical kinesis" or motivational modulation of movement speed in PD may be differently enhanced, depending on treatment modality.

Apathy is one of the recognized side-effects of STN DBS in PD, partly attributed to the reduction of dopaminergic medication and partly considered to be induced by STN DBS (Castrioto, Lhommee, Moro, & Krack, 2014). Apathy is considered a motivational deficit, associated with inhibition of self-generated activity, emotional indifference, and lack of cognitive processing (psychic ‘akinesia’ or vacuum). Despite higher levels of self-reported apathy relative to healthy controls (6 out of 10 patients had relatively high scores >39) on the apathy scale,(Table 1) , the patients in our sample nevertheless showed motivational modulation of movement speed both with STN DBS ON and OFF and enhanced responsiveness to the value of monetary incentive with STN stimulation. These points to the dissociation between the clinical manifestations of deficient motivation in everyday situations represented by self-reported apathy and experimental modulation of speed of responding to external

stimuli with monetary incentive. Future investigation of this dissociation is of interest and may have value in harnessing external stimuli with incentive value in the clinical management of apathy following STN DBS surgery.

5. Conclusions

Our results provide evidence that motivational modulation of movement speed in PD is maintained with STN-DBS, and in fact STN stimulation may have a further energizing effect on movement initiation speed with greater incentive value. This effect may partly account for the increased impulsivity documented with STN-DBS in PD.

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References

Albin, R. L., Young, A. B., & Penney, J. B. (1989). The functional anatomy of basal ganglia disorders. Trends Neurosci, 12, 366-375.

Albin, R. L., Young, A. B., & Penney, J. B. (1995). The functional anatomy of disorders of the basal ganglia. Trends Neurosci, 18, 63-64.

Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci, 9, 357-381.

Amami, P., Dekker, I., Piacentini, S., Ferre, F., Romito, L. M., Franzini, A., Foncke, E. M., & Albanese, A. (2015). Impulse control behaviours in patients with Parkinson's disease after subthalamic deep brain stimulation: de novo cases and 3-year follow-up. J Neurol Neurosurg Psychiatry, 86, 562-564.

Baunez, C., Nieoullon, A., & Amalric, M. (1995). In a rat model of parkinsonism, lesions of the subthalamic nucleus reverse increases of reaction time but induce a dramatic premature responding deficit. J Neurosci, 15, 6531-6541.

Baunez, C., & Robbins, T. W. (1997). Bilateral lesions of the subthalamic nucleus induce multiple deficits in an attentional task in rats. Eur J Neurosci, 9, 2086-2099.

Beck, A. T., & Beamesderfer, A. (1974). Assessment of depression: the depression inventory. Mod Probl Pharmacopsychiatry, 7, 151-169.

Castelli, L., Lanotte, M., Zibetti, M., Caglio, M., Rizzi, L., Ducati, A., Bergamasco, B., & Lopiano, L. (2007). Apathy and verbal fluency in STN-stimulated PD patients. An observational follow-up study. J Neurol, 254, 1238-1243.

Castrioto, A., Lhommee, E., Moro, E., & Krack, P. (2014). Mood and behavioural effects of subthalamic stimulation in Parkinson's disease. Lancet Neurol, 13, 287-305.

Chong, T. T., Bonnelle, V., Manohar, S., Veromann, K. R., Muhammed, K., Tofaris, G. K., Hu, M., & Husain, M. (2015). Dopamine enhances willingness to exert effort for reward in Parkinson's disease. Cortex, 69, 40-46.

Chou, K. L., Persad, C. C., & Patil, P. G. (2012). Change in fatigue after bilateral subthalamic nucleus deep brain stimulation for Parkinson's disease. Parkinsonism Relat Disord, 18, 510-513.

Cury, R. G., Galhardoni, R., Fonoff, E. T., Dos Santos Ghilardi, M. G., Fonoff, F., Arnaut, D., Myczkowski, M. L., Marcolin, M. A., Bor-Seng-Shu, E., Barbosa, E. R., Teixeira, M. J., & Ciampi de Andrade, D. (2014). Effects of deep brain stimulation on pain and other nonmotor symptoms in Parkinson disease. Neurology, 83, 1403-1409.

Czernecki, V., Pillon, B., Houeto, J. L., Welter, M. L., Mesnage, V., Agid, Y., & Dubois, B. (2005). Does bilateral stimulation of the subthalamic nucleus aggravate apathy in Parkinson's disease? J Neurol Neurosurg Psychiatry, 76, 775-779.

DeLong, M., & Wichmann, T. (2010). Changing views of basal ganglia circuits and circuit disorders. Clin EEG Neurosci, 41, 61-67.

DeLong, M. R. (1990). Primate models of movement disorders of basal ganglia origin. Trends Neurosci, 13, 281-285.

Demetriades, P., Rickards, H., & Cavanna, A. E. (2011). Impulse control disorders following deep brain stimulation of the subthalamic nucleus in Parkinson's disease: clinical aspects. Parkinsons Dis, 2011, 658415.

Evens, R., Stankevich, Y., Dshemuchadse, M., Storch, A., Wolz, M., Reichmann, H., Schlaepfer, T. E., Goschke, T., & Lueken, U. (2015). The impact of Parkinson's disease and subthalamic deep brain stimulation on reward processing. Neuropsychologia, 75, 11-19.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res, 12, 189-198.

Frank, M. J. (2006). Hold your horses: a dynamic computational role for the subthalamic nucleus in decision making. Neural Netw, 19, 1120-1136.

Frank, M. J., Samanta, J., Moustafa, A. A., & Sherman, S. J. (2007). Hold your horses: impulsivity, deep brain stimulation, and medication in parkinsonism. Science, 318, 1309-1312.

Gervais-Bernard, H., Xie-Brustolin, J., Mertens, P., Polo, G., Klinger, H., Adamec, D., Broussolle, E., & Thobois, S. (2009). Bilateral subthalamic nucleus stimulation in advanced Parkinson's disease: five year follow-up. J Neurol, 256, 225-233.

Glickstein, M., & Stein, J. (1991). Paradoxical movement in Parkinson's disease. Trends Neurosci, 14, 480-482.

Goetz, C. G., Tilley, B. C., Shaftman, S. R., Stebbins, G. T., Fahn, S., Martinez-Martin, P., Poewe, W., Sampaio, C., Stern, M. B., Dodel, R., Dubois, B., Holloway, R., Jankovic, J., Kulisevsky, J., Lang, A. E., Lees, A., Leurgans, S., LeWitt, P. A., Nyenhuis, D., Olanow, C. W., Rascol, O., Schrag, A., Teresi, J. A., van Hilten, J. J., LaPelle, N., & Movement Disorder Society, U. R. T. F. (2008). Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord, 23, 2129-2170.

Griffin, H. J., Greenlaw, R., Limousin, P., Bhatia, K., Quinn, N. P., & Jahanshahi, M. (2011). The effect of real and virtual visual cues on walking in Parkinson's disease. J Neurol, 258, 991-1000.

Jahanshahi, M. (2013). Effects of deep brain stimulation of the subthalamic nucleus on inhibitory and executive control over prepotent responses in Parkinson's disease. Front Syst Neurosci, 7, 118.

Jahanshahi, M., Obeso, I., Rothwell, J. C., & Obeso, J. A. (2015). A fronto-striato-subthalamic-pallidal network for goal-directed and habitual inhibition. Nat Rev Neurosci, 16, 719-732.

Kim, H. J., Jeon, B. S., & Paek, S. H. (2015). Nonmotor Symptoms and Subthalamic Deep Brain Stimulation in Parkinson's Disease. J Mov Disord, 8, 83-91.

Kluger, B. M., Parra, V., Jacobson, C., Garvan, C. W., Rodriguez, R. L., Fernandez, H. H., Fogel, A., Skoblar, B. M., Bowers, D., & Okun, M. S. (2012). The prevalence of fatigue following deep brain stimulation surgery in Parkinson's disease and association with quality of life. Parkinsons Dis, 2012, 769506.

Kojovic, M., Mir, P., Trender-Gerhard, I., Schneider, S. A., Parees, I., Edwards, M. J., Bhatia, K. P., & Jahanshahi, M. (2014). Motivational modulation of bradykinesia in Parkinson's disease off and on dopaminergic medication. J Neurol, 261, 1080-1089.

Krack, P., Batir, A., Van Blercom, N., Chabardes, S., Fraix, V., Ardouin, C., Koudsie, A., Limousin, P. D., Benazzouz, A., LeBas, J. F., Benabid, A. L., & Pollak, P. (2003). Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med, 349, 1925-1934.

Lambert, C., Zrinzo, L., Nagy, Z., Lutti, A., Hariz, M., Foltynie, T., Draganski, B., Ashburner, J., & Frackowiak, R. (2012). Confirmation of functional zones within the human subthalamic nucleus: patterns of connectivity and sub-parcellation using diffusion weighted imaging. Neuroimage, 60, 83-94.

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.

Lilleeng, B., Gjerstad, M., Baardsen, R., Dalen, I., & Larsen, J. P. (2015). The long-term development of non-motor problems after STN-DBS. Acta Neurol Scand, 132, 251-258.

Lim, S. Y., O'Sullivan, S. S., Kotschet, K., Gallagher, D. A., Lacey, C., Lawrence, A. D., Lees, A. J., O'Sullivan, D. J., Peppard, R. F., Rodrigues, J. P., Schrag, A., Silberstein, P., Tisch, S., & Evans, A. H. (2009). Dopamine dysregulation syndrome, impulse control disorders and punding after deep brain stimulation surgery for Parkinson's disease. J Clin Neurosci, 16, 1148-1152.

Lule, D., Heimrath, J., Pinkhardt, E. H., Ludolph, A. C., Uttner, I., & Kassubek, J. (2012). Deep brain stimulation and behavioural changes: is comedication the most important factor? Neurodegener Dis, 9, 18-24.

Mallet, L., Schupbach, M., N'Diaye, K., Remy, P., Bardinet, E., Czernecki, V., Welter, M. L., Pelissolo, A., Ruberg, M., Agid, Y., & Yelnik, J. (2007). Stimulation of subterritories of the subthalamic nucleus reveals its role in the integration of the emotional and motor aspects of behavior. Proc Natl Acad Sci U S A, 104, 10661-10666.

Marin, R. S., Biedrzycki, R. C., & Firinciogullari, S. (1991). Reliability and validity of the Apathy Evaluation Scale. Psychiatry Res, 38, 143-162.

McDonald, L. M., Griffin, H. J., Angeli, A., Torkamani, M., Georgiev, D., & Jahanshahi, M. (2015). Motivational Modulation of Self-Initiated and Externally Triggered Movement Speed Induced by Threat of Shock: Experimental Evidence for Paradoxical Kinesis in Parkinson's Disease. PLoS One, 10, e0135149.

Monakow, K. H., Akert, K., & Kunzle, H. (1978). Projections of the precentral motor cortex and other cortical areas of the frontal lobe to the subthalamic nucleus in the monkey. Exp Brain Res, 33, 395-403.

Moum, S. J., Price, C. C., Limotai, N., Oyama, G., Ward, H., Jacobson, C., Foote, K. D., & Okun, M. S. (2012). Effects of STN and GPi deep brain stimulation on impulse control disorders and dopamine dysregulation syndrome. PLoS One, 7, e29768.

Nambu, A., Tokuno, H., & Takada, M. (2002). Functional significance of the cortico-subthalamo-pallidal 'hyperdirect' pathway. Neurosci Res, 43, 111-117.

Oyama, G., Shimo, Y., Natori, S., Nakajima, M., Ishii, H., Arai, H., & Hattori, N. (2011). Acute effects of bilateral subthalamic stimulation on decision-making in Parkinson's disease. Parkinsonism Relat Disord, 17, 189-193.

Pagonabarraga, J., Kulisevsky, J., Strafella, A. P., & Krack, P. (2015). Apathy in Parkinson's disease: clinical features, neural substrates, diagnosis, and treatment. Lancet Neurol, 14, 518-531.

Parsons, T. D., Rogers, S. A., Braaten, A. J., Woods, S. P., & Troster, A. I. (2006). Cognitive sequelae of subthalamic nucleus deep brain stimulation in Parkinson's disease: a meta-analysis. Lancet Neurol, 5, 578-588.

Rogers, R. D., Wielenberg, B., Wojtecki, L., Elben, S., Campbell-Meiklejohn, D., & Schnitzler, A. (2011). Deep brain stimulation of the subthalamic nucleus transiently enhances loss-chasing behaviour in patients with Parkinson's disease. Exp Neurol, 231, 181-189.

Saint-Cyr, J. A., Trepanier, L. L., Kumar, R., Lozano, A. M., & Lang, A. E. (2000). Neuropsychological consequences of chronic bilateral stimulation of the subthalamic nucleus in Parkinson's disease. Brain, 123 (Pt 10), 2091-2108.

Sauleau, P., Eusebio, A., Vandenberghe, W., Nuttin, B., & Brown, P. (2009). Deep brain stimulation modulates effects of motivation in Parkinson's disease. Neuroreport, 20, 622-626.

Schuepbach, W. M., Rau, J., Knudsen, K., Volkmann, J., Krack, P., Timmermann, L., Halbig, T. D., Hesekamp, H., Navarro, S. M., Meier, N., Falk, D., Mehdorn, M., Paschen, S., Maarouf, M., Barbe, M. T., Fink, G. R., Kupsch, A., Gruber, D., Schneider, G. H., Seigneuret, E., Kistner, A., Chaynes, P., Ory-Magne, F., Brefel Courbon, C., Vesper, J., Schnitzler, A., Wojtecki, L., Houeto, J. L., Bataille, B., Maltete, D., Damier, P., Raoul, S., Sixel-Doering, F., Hellwig, D., Gharabaghi, A., Kruger, R., Pinsker, M. O., Amtage, F., Regis, J. M., Witjas, T., Thobois, S., Mertens, P., Kloss, M., Hartmann, A., Oertel, W. H., Post, B., Speelman, H., Agid, Y., Schade-Brittinger, C., Deuschl, G., & Group, E. S. (2013). Neurostimulation for Parkinson's disease with early motor complications. N Engl J Med, 368, 610-622.

Serranova, T., Jech, R., Dusek, P., Sieger, T., Ruzicka, F., Urgosik, D., & Ruzicka, E. (2011). Subthalamic nucleus stimulation affects incentive salience attribution in Parkinson's disease. Mov Disord, 26, 2260-2266.

Shiner, T., Seymour, B., Symmonds, M., Dayan, P., Bhatia, K. P., & Dolan, R. J. (2012). The effect of motivation on movement: a study of bradykinesia in Parkinson's disease. PLoS One, 7, e47138.

Uslaner, J. M., & Robinson, T. E. (2006). Subthalamic nucleus lesions increase impulsive action and decrease impulsive choice - mediation by enhanced incentive motivation? Eur J Neurosci, 24, 2345-2354.

van Wouwe, N. C., Ridderinkhof, K. R., van den Wildenberg, W. P., Band, G. P., Abisogun, A., Elias, W. J., Frysinger, R., & Wylie, S. A. (2011). Deep brain stimulation of the subthalamic nucleus improves reward-based decision-learning in Parkinson's disease. Front Hum Neurosci, 5, 30.

Williams, A., Gill, S., Varma, T., Jenkinson, C., Quinn, N., Mitchell, R., Scott, R., Ives, N., Rick, C., Daniels, J., Patel, S., Wheatley, K., & Group, P. S. C. (2010). Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial. Lancet Neurol, 9, 581-591.

Figure legends:

Figure 1: Initiation time (IT) data for PD patients with STN DBS OFF and ON and for healthy participants in the unwarned simple reaction time (uSRT) and warned simple reaction time (wSRT) tasks. Error bars are standard error of the mean. Data presented are the raw data. Blocks 1 and Block 2 are unrewarded blocks; Blocks 3 and block 4 are rewarded blocks.

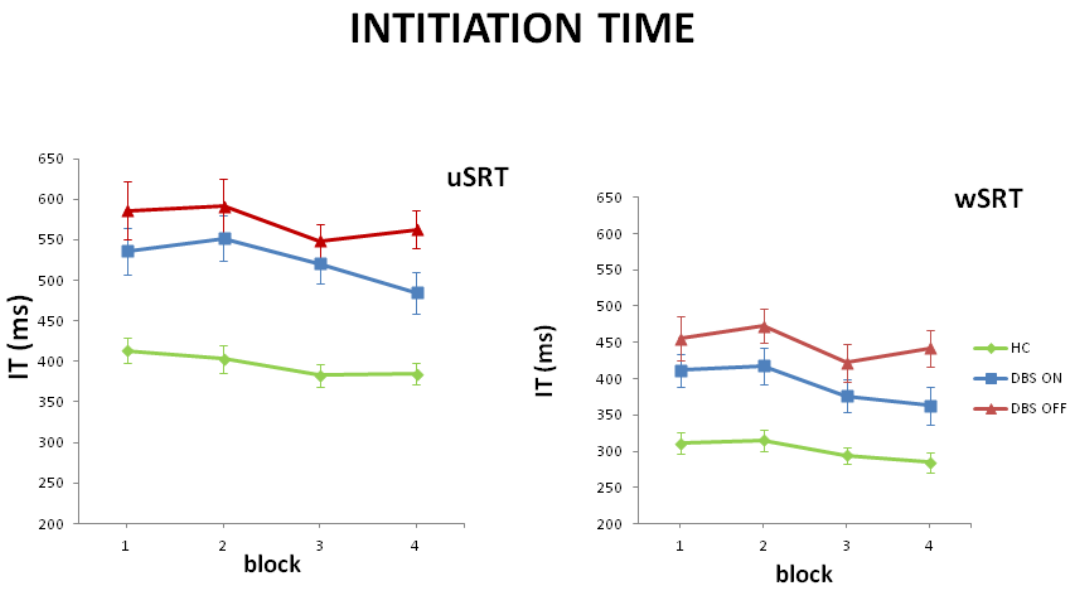


Figure 2: Initiation time (IT) improvement in the two rewarded blocks (in response to increasing reward magnitude), relative to unrewarded blocks. Data are presented as average of uSRT and wSRT. PD patients with STN DBS ON show greater improvement of IT in response to higher (100p) reward magnitude compared to DBS OFF condition. Error bars are standard error of the mean. * indicates $p<0.05$

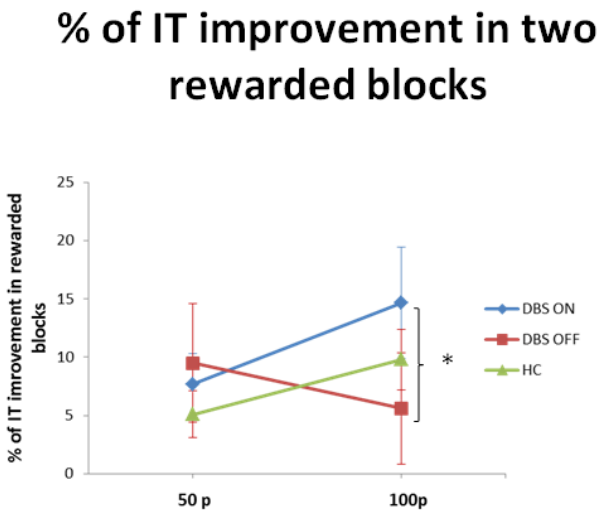


Figure 3: Movement time (MT) data for PD patients with STN DBS OFF and ON and for healthy participants in the unwarned simple reaction time (uSRT) and warned simple reaction time (wSRT) tasks. Error bars are standard error of the mean. Data presented are the raw data. Blocks 1 and Block 2 are unrewarded blocks; Blocks 3 and block 4 are rewarded blocks.

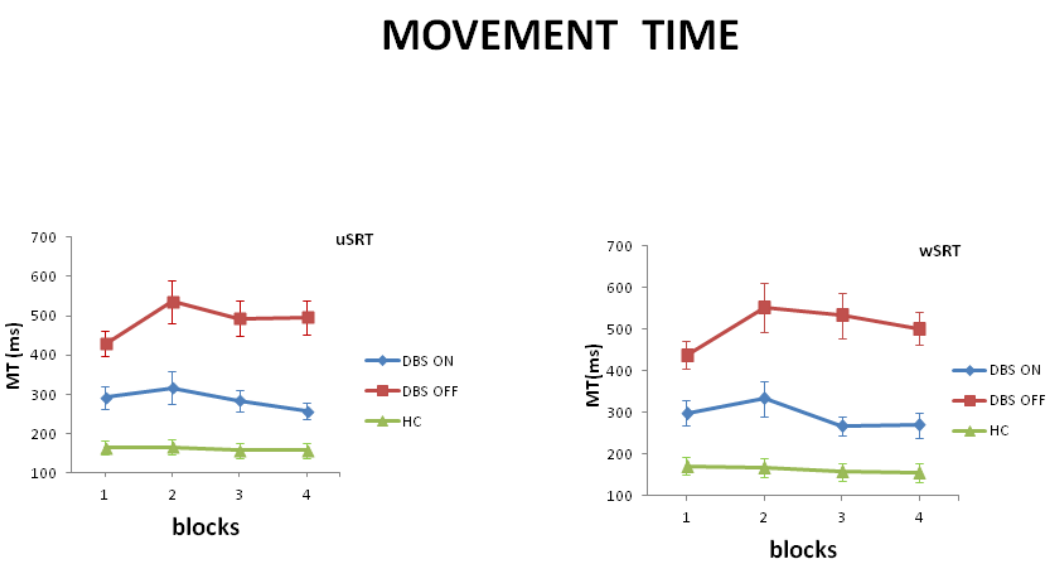
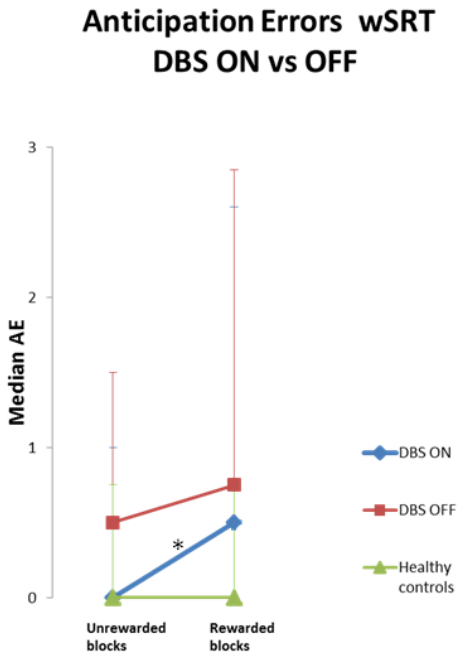


Figure 4: Anticipation errors (AE) in the warned SRT task in rewarded (average of blocks 1 and 2) and unrewarded blocks (average of blocks 3 and 4) for PD patients and healthy controls. PD patients with STN DBS ON have significantly increased number of AEs in the presence of reward. AEs are presented as a MEAN with a range. * indicates $p<0.05$.



Supplementary figure: Illustration of the simple reaction time task, showing the sequence of events presented on the computer screen at different stages of the unwarned and warned trials.

Table 1 : Parkinsons‘ s Disease patients -demographic and clinical characteristics and stimulation parameters

Sex	Age	Disease duration	Voltage(V)/ frequency(Hz) / pulse width(µs) L STN	Voltage(V)/ frequency(Hz) / pulse width(µs) R STN	UPDRS OFF	UPDRS ON	MMSE	MAS	BDI
M	78	16	3.30/130/60	3.30/130/60	76	36	25	49	11
M	67	24	4.20/130/60	4.10/130/60	42	25	30	30	6
M	61	12	2.60/130/60	3.10/130/60	34	22	28	46	14
M	55	9	2.20/130/60	2.20/130/60	33	17	30	33	2
M	50	15	3.60/130/60	3.10/130/60	54	18	30	40	10
M	55	15	4.50/130/60	4.50/130/60	22	11	29	36	7
M	53	8	2.90/130/60	3.20/130/60	26	18	30	23	7
M	57	15	3.70/185/60	4.50/185/60	50	31	30	44	8
M	39	9	2.00/130/60	3.40/130/60	43	17	30	43	14
F	65	17	1.80/130/60	2.00/130/60	36	24	29	41	9
Average	58	14	3.08/135.5/60	3.34/135.5/60	41.6	21.9	29.1	38.5	8.8
SEM	3.45	1.56	0.29/0.43/0	0.27/0.43/0	5.2	2.5	0.5	2.5	1.2

Abbreviations: M, male; F, female; STN, subthalamic nucleus; Motor section of UPDRS, United Parkinson Disease Scale (OFF, off DBS; ON, on DBS); MMSE, Mini Mental Status Examination; MAS, Marin Apathy Scale ; BDI, Beck Depression Inventory

Table 2 : Parkinsons‘ s Disease patients and healthy controls; group comparisons of demographic data and questionairres scores

Group	Age	Education (years)	Right handedness (%)	MMSE	MAS	BDI
PD patients	58 (3.3)	14.4 (0.9)	86.7(5.5)	29.1 (0.5)	38.5(2.5)	8.8(1.2)
Controls	57 (4.6)	15.4 (0.8)	88.3(3)	29.4(0.3)	30.1(1.53)	5.8(1.6)
Statistics	p=0.9	p=0.5	p=0.8	p=0.6	p=0.01	p=0.2

Abbreviations: MMSE, Mini Mental Status Examination; MAS, Marin Apathy Scale ; BDI, Beck Depression Inventory

Table 3. Median number (and the range) of anticipation errors and long responses in PD patients and healthy participants across non-rewarded and rewarded blocks

		BLOCK 1				BLOCK 2				BLOCK 3				BLOCK 4			
		AE		LR		AE		LR		AE		LR		AE		LR	
		uSRT	wSRT	uSRT	wSRT	uSRT	wSRT	uSRT	wSRT	uSRT	wSRT	uSRT	wSRT	uSRT	wSRT	uSRT	wSRT
DBS STN ON	Median	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Interval	0-0	0-3	0-1	0-1	0-0	0-3	0-1	0-1	0-0	0-4	0-1	0-0	0-0	0-3	0-2	0-2
DBS STN OFF	Median	0	0	0	0.5	0	0	0	0	0	0	0	0	0	1	0	0
	Interval	0-2	0-2	0-4	0-1	0-1	0-3	0-2	0-2	0-1	0-4	0-1	0-1	0-2	0-5	0-1	0-1
HEALTHY PARTICIPANTS	Median	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Interval	0-0	0-1	0-2	0-0	0-0	0-2	0-0	0-1	0-0	0-1	0-0	0-0	0-0	0-1	0-1	0-0

Abbreviations: AE, anticipation errors; LR, long responses; uSRT, unwarned simple reaction time; wSRT, warned simple reaction time.

Highlights:

- Monetary incentive improves movement initiation in Parkinson's disease
- This reward effect is present in patients with STN-DBS, both on and off stimulation
- Patients show greater responsivity to higher reward value with STN-DBS ON vs. DBS OFF
- STN stimulation induces impulsive premature responses with the prospect of reward
- The STN is involved in motivational modulation of motor behaviour