



HAL
open science

Subthalamic nucleus stimulation, dopaminergic treatment and impulsivity in Parkinson's disease

Frédérique Fluchère, Boris Burle, Franck Vidal, Wery van den Wildenberg, Tatiana Witjas, Alexandre Eusebio, Jean-Philippe Azulay, Thierry Hasbroucq

► To cite this version:

Frédérique Fluchère, Boris Burle, Franck Vidal, Wery van den Wildenberg, Tatiana Witjas, et al.. Subthalamic nucleus stimulation, dopaminergic treatment and impulsivity in Parkinson's disease. *Neuropsychologia*, inPress, 10.1016/j.neuropsychologia.2018.02.016 . hal-01735291

HAL Id: hal-01735291

<https://hal.science/hal-01735291v1>

Submitted on 15 Mar 2018

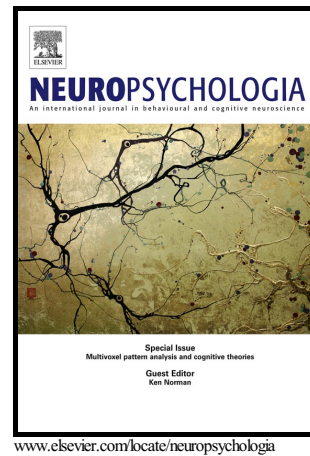
HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Author's Accepted Manuscript

Subthalamic nucleus stimulation, dopaminergic treatment and impulsivity in Parkinson's disease

Frédérique Fluchère, Boris Burle, Franck Vidal, Wery van den Wildenberg, Tatiana Witjas, Alexandre Eusebio, Jean-Philippe Azulay, Thierry Hasbroucq



PII: S0028-3932(18)30073-3
DOI: <https://doi.org/10.1016/j.neuropsychologia.2018.02.016>
Reference: NSY6689

To appear in: *Neuropsychologia*

Received date: 3 August 2017
Revised date: 10 February 2018
Accepted date: 12 February 2018

Cite this article as: Frédérique Fluchère, Boris Burle, Franck Vidal, Wery van den Wildenberg, Tatiana Witjas, Alexandre Eusebio, Jean-Philippe Azulay and Thierry Hasbroucq, Subthalamic nucleus stimulation, dopaminergic treatment and impulsivity in Parkinson's disease, *Neuropsychologia*, <https://doi.org/10.1016/j.neuropsychologia.2018.02.016>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting galley proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Subthalamic nucleus stimulation, dopaminergic treatment and impulsivity in Parkinson's disease

Frédérique Fluchère^{a,b*}, Borís Burle^a, Franck Vidal^a, Wery van den Wildenberg^{c,d}, Tatiana Witjas^b, Alexandre Eusebio^{b,e}, Jean-Philippe Azulay^{b,e}, Thierry Hasbroucq^a

^aLaboratoire de Neurosciences Cognitives, Fédération de Recherche Comportement-Cerveau-Cognition, Aix-Marseille Université, Centre National de la Recherche Scientifique, Marseille, France.

^bDepartment of Neurology and Movement Disorders, Aix-Marseille Université, Pôle de Neurosciences Cliniques, Assistance Publique-Hôpitaux de Marseille, La Timone, Marseille, France.

^cDepartment of Psychology, University of Amsterdam, Amsterdam, the Netherlands

^dAmsterdam Brain & Cognition, University of Amsterdam, Amsterdam, the Netherlands

^eInstitut des Neurosciences de la Timone, Aix-Marseille Université, Centre National de la Recherche Scientifique, Marseille, France

*Corresponding author: APHM, La Timone, Department of Neurology and Movement Disorders, Pôle de Neurosciences cliniques, 13385 Marseille cedex 05, France. Tel. +33491384333; fax +33491384336. frederique.fluchere@ap-hm.fr

Abstract**Background**

Deep brain stimulation of the subthalamic nucleus (STN DBS) is known to increase response speed and lower response accuracy in Parkinson's disease (PD) patients. It has been proposed that this speed-accuracy tradeoff is due to enhanced sensitivity of the motor system to sensory information. An alternative possibility is that this effect is due to weakened suppressive processes. The two alternative interpretations can be tested by analyzing the electromyographic activity (EMG) of the response agonists when the patients perform conflict reaction time tasks. In those tasks, fast subthreshold muscle impulses often occur in the agonist of the incorrect response. These impulses are *partial errors* that are suppressed before being behaviourally committed.

Material and Methods

Here we analyzed the EMG of the response agonists recorded while sixteen PD patients performed a Simon task that elicits prepotent response tendencies so as to decipher (i) whether STN DBS affects the expression and/or suppression of subthreshold muscle impulses that are critical for action control and (ii) the interaction between dopaminergic treatment and STN DBS. The patients were tested On and Off STN DBS and On and Off dopaminergic medication in a full factorial design.

Results

STN DBS not only impaired the proficiency to suppress subliminal action impulses ($p = 0.01$) but also favoured the muscular expression of fast incorrect impulses ($p < 0.001$). Dopaminergic treatment only affected the action impulses suppression ($p = 0.02$) and did not change the effect of STN DBS on impulsive action control.

Conclusion

Contrary to a recent proposal, STN DBS impaired rather than improved action control by weakening erroneous impulse suppression, whether the patients were On or Off their usual medication. These findings are discussed in light of a recent proposal (Servant M, White C, Montagnini A, Burle B, 2015) that reconciles partial errors with accumulation-to-bound models of decision making. Our results suggest that medication specifically lowers the mechanical threshold while STN DBS lowers the mechanical threshold and to a lesser extent the EMG-threshold.

Keywords

Parkinson, STN stimulation, dopamine, impulsivity, motor control, decision's threshold

Abbreviations

DBS, Deep brain stimulation; PD, Parkinson's disease; STN, Subthalamic nucleus

1. Introduction

In Parkinson's disease (PD), deep brain stimulation (DBS) of the subthalamic nucleus (STN) alleviates the patients' cardinal motor symptoms and improves their quality of life (Limousin et al., 1995; Martínez-Martín et al., 2002). However, growing evidence suggests that this surgical treatment can increase action impulsivity defined as a predisposition toward rapid, unplanned actions to internal or external stimuli (Ballanger et al., 2009; for a review see Jahanshahi, 2013 and 2015). This view is consistent with the notion that STN plays a key role in inhibition processes (for reviews, see Jahanshahi, 2013 and 2015).

Notably, this effect has been experimentally studied and modelled in the context of the choice reaction time paradigm. There is general agreement that STN DBS increases response speed and lowers response accuracy (e.g., Jahanshahi et al., 2013 and 2015). Such a speed-accuracy tradeoff that is thought to reflect an increase in action impulsivity is captured by the quantitative model of Wiecki and Frank (2013). This model is based on the drift diffusion principle (Ratcliff, 1978) according to which information processing is amenable to a gradual process based on the accumulation of information over time, a given overt response being emitted as soon as the accumulation reaches a decision threshold. Recent intra-cerebral recordings in PD patients support the notion that STN mediates this decision threshold's

modulation: STN low-frequency oscillatory activity predicts adjustments of decision thresholds before subjects make a response (Herz et al, 2016 et 2017). According to Wiecki and Frank (2013), by reducing STN outputs to the pallidum resulting in a lower inhibition of the thalamus, DBS would lower the decision threshold thereby increasing response speed, but also lowering response accuracy. As a consequence, STN DBS yields impulsive behaviours.

Wylie et al. (2010) adopted a behavioral approach to address STN DBS effects on action impulsivity in PD. These authors used the Simon task that provides experimental contexts for analyzing how irrelevant external stimulus information elicits response impulses that interfere with goal-directed actions (van den Wildenberg et al., 2010). In the most common version of the Simon task, the participants choose between a left- and a right-hand key press according to the color of a visual stimulus presented a few degrees either to the left or the right of a central fixation point. The performance expressed both in terms of error rate and mean reaction time is better when the required response corresponds spatially to the irrelevant stimulus location (congruent association) than when it does not correspond (incongruent association), reflecting an automatic activation of the response ipsilateral to the stimulus. Wylie et al. (2010) showed that in the Simon task, the speed-accuracy tradeoff induced by STN DBS is specifically due to an increase in the occurrence of fast overt choice errors for incongruent associations. This finding led them to conclude that this treatment increases the capture of the patients' motor system by impulses triggered by the irrelevant stimulus location (see Ridderinkhof, 2002). Moreover, Wylie et al. observed that for correct trials, the size of the interference on RT decreased as response speed slowed, and concluded that STN DBS improves inhibitory control over involuntary response tendencies on correct trials (see Ridderinkhof, 2002).

Note that these interpretations only hold if the amount of fast errors is solely determined by the strength of the response capture. Recent data, however, suggests that it

might also be affected by corrective processes (see e.g. Spieser et al., 2015). Many correct response trials contain subthreshold muscle activity in the incorrect hand, a so-called *partial EMG error* (Hasbroucq et al., 1999; Burle et al., 2002). While reflecting impulsive response capture, such partial EMG errors are suppressed before being committed behaviourally. Hence, an increase in fast *overt* response errors may also be due to a reduced capacity to overcome response capture (see Spieser et al., 2015). Note that Wiecki and Frank's (2013) model and all its formal cognates (e.g., Ratcliff & Smith, 2004, Hubner et al., 2010, White et al., 2011) assume that motor activity is engaged in an all-or-none fashion once the decision threshold is reached, an assumption contradicted by the mere occurrence of partial EMG errors. To reconcile accumulation-to-bound model with partial errors, Servant et al. (2015) introduced an EMG-threshold, above which EMG activity is produced. The EMG-threshold being lower than the mechanical overt response threshold leaves space for correction to occur (see also Burle et al., 2008). One way to probe the relative positions of the two thresholds is to fractionate the reaction time based on EMG into the "pre-motor time" (from stimulus onset to EMG onset) and the "motor time" (between EMG onset and recorded mechanical response) (Hasbroucq et al., 1995). Importantly, adding constraints based on the observed EMG pattern allows distinguishing models that make virtually identical predictions based on behavior (Servant et al., 2015).

We anticipate that studying EMG activity according to the approach outlined above will improve our understanding of Parkinsonian pathophysiology (Fluchère et al., 2015). Here, we combined behavioral methods with EMG analyses to study the influence of STN DBS on the expression and suppression of incorrect action impulses. Based on EMG activity, three categories of trials were distinguished: (i) pure correct trials, i.e., without response-related EMG activity in the incorrect hand; (ii) partial error trials, i.e., trials on which subthreshold but transient muscle activity in the incorrect hand precedes the correct response;

and (iii) incorrect trials, associated with an incorrect overt response (Hasbroucq et al., 1999). A higher incidence of incorrect response activations (including both overt errors and partial EMG errors) indicates increased impulse expression (Hasbroucq et al., 2009). Of particular interest is the so-called *correction ratio*; the ratio between the number of partial EMG errors and the number of incorrect activations, representing the ability to suppress covert incorrect response impulses to prevent overt errors (Burle et al., 2002). Lower correction ratios reflect less proficient suppression of impulsive errors. By analyzing EMG activity during performance of the Simon task that requires overriding erroneous response tendencies, we could assess the effects of STN DBS and dopaminergic treatment on two components of action impulsivity (DeYoung, 2011) that are otherwise not dissociable: expression and suppression of subthreshold impulsive errors. This leads to the following predictions. If STN DBS increases the expression of impulses, it should increase the number of incorrect activations (sum of full performance errors and of partial EMG errors). In contrast, if STN DBS impairs impulse suppression (Frank et al., 2007, Ballanger et al., 2009) as does PD patients' medication (Fluchère et al., 2015), it should decrease the correction ratio.

Finally, as noted by Wylie et al. (2010), the interaction between STN DBS and dopaminergic treatment has not yet been studied empirically. The second aim of the present study was to address this issue by analyzing the performance and EMG activity of PD patients On and Off STN DBS and On and Off dopaminergic medication in a full factorial design. The factorial design of the present study might reveal interactions between this surgical treatment and the patient's dopaminergic medication on action control.

2. Material and methods

2.1. Subjects

Sixteen patients (four women) with idiopathic PD who had been treated successfully with STN DBS participated in this study. The demographic characteristics, usual medication, STN DBS settings and clinical data of the patients are presented in Tables 1 and 2. All gave

written informed consent according to the convention of Helsinki and the study was approved by the local research ethics committee. The electrodes (model 3389, Medtronic, Inc. Minneapolis) were implanted bilaterally. Details concerning the neurosurgical procedure have been published elsewhere (Fluchère et al., 2014). Thirteen patients were right-handed and three were left-handed, according to the Edinburgh Handedness inventory (Oldfield, 1971). Age varied between 46 and 76 years ($M = 64$ years, $SD = 8$ years). The mean disease duration was 13 years ($SD = 5$ years). The stimulation parameters and medication dosage were individually set in order to achieve optimal therapeutic effects.

Table 1 Demographic characteristics, levodopa equivalent daily dose, and STN DBS settings of the patients

Patients	Gender	Age (years)	PD duration / Delay post surgery (years)	Hoehn and Yahr stage (Off / On)	LEDD (mg)	STN DBS settings	
						Rate(Hz)/Pulse width (μ s)/ Voltage(V)	Right electrode
1	M	57	7 / 1	2.5 / 2.5	350	130 Hz / 60 μ s / 2,8 V	130 Hz / 60 μ s / 2,8 V
2	M	61	12 / 5	2 / 1	1000	130 Hz / 60 μ s / 2,7 V	130 Hz / 60 μ s / 3,2 V
3	M	55	21 / 5	3 / 2.5	700	130 Hz / 60 μ s / 3 V	130 Hz / 60 μ s / 2,3 V
4	M	65	9 / 1	2.5 / 1	600	185 Hz / 60 μ s / 2,8 V	185 Hz / 60 μ s / 1,8 V
5	W	66	23 / 5	2 / 2	530	130 Hz / 60 μ s / 3 V	130 Hz / 60 μ s / 3 V
6	M	70	10 / 3	3 / 3	600	130 Hz / 60 μ s / 2,8 V	130 Hz / 60 μ s / 2,4 V
7	M	66	16 / 5	2.5 / 2	600	130 Hz / 60 μ s / 3,3 V	130 Hz / 60 μ s / 3 V
8	M	62	9 / 1	2 / 2	500	190 Hz / 60 μ s / 2,8 V	190 Hz / 60 μ s / 2,4 V
9	M	69	18 / 5	3 / 3	950	130 Hz / 60 μ s / 3 V	130 Hz / 60 μ s / 3 V
10	M	66	14 / 3	3 / 2	970	130Hz / 60 μ s / 3 V	130Hz / 60 μ s / 2,9 V
11	W	57	8 / 1	3 / 1	250	170 Hz / 60 μ s / 3,1 V	170 Hz / 60 μ s / 2,5 V
12	M	72	16 / 3	3 / 2.5	500	130 Hz / 60 μ s / 2,8 V	130 Hz / 60 μ s / 2,6 V
13	W	69	14 / 1	3 / 2	450	130 Hz / 60 μ s / 2,5 V	130 Hz / 60 μ s / 2,5 V
14	W	76	13 / 5	2.5 / 2.5	950	130 Hz / 60 μ s / 2,7 V	130 Hz / 60 μ s / 3 V
15	M	46	11 / 2	2 / 0	400	190 Hz / 90 μ s / 2,4 V	190 Hz / 90 μ s / 3 V
16	M	67	10 / 0.6	2 / 0	800	130 Hz / 60 μ s / 2,5 V	130 Hz / 60 μ s / 2,5 V

Sixteen patients (4 women) with idiopathic Parkinson's disease were tested in this study. They were treated with STN DBS for at least 6 months ($M = 3$ years, $SD = 2$ years), associated with an oral dopaminergic treatment

(levodopa ± dopaminergic agonist). All patients exhibited a clinically effective and stable response to STN DBS and ambulated independently. They were aged between 46 and 76 years ($M = 64$ years, $SD = 8$ years), the mean disease duration was 13 years ($SD = 5$ years), and the mean delay post-surgery was 3 years ($SD = 2$ years). Three patients were left-handed. The stimulation parameters and medication dosage were established in order to achieve the best therapeutic effect for each patient. Patients no. 4, 8, 11, 15 were stimulated at very high frequency due to important tremor.

M = man; W = woman; PD = Parkinson's disease; DPS = delay post-surgery; LEDD: levodopa equivalent daily dose.

Neuropsychological (Mini-Mental State Examination and Mattis scale) and mood (Beck Depression Inventory II) tests were performed to exclude patients with significant cognitive impairments or major depressive syndrome. As recommended by the Movement Disorder Society Task Force, the cutoff of 26 out of 30, 136 out of 144, and 20 out of 62 were used respectively for the MMSE, the Mattis scale, and for the Beck Depression Inventory. Impulse control disorders were also screened by a specific interview performed by a psychiatric specialized in movement disorders and by the Modified Minnesota Impulsive Disorders Interview (Christenson et al,1994). None of the included patients had this kind of trouble at the time of the study. The other exclusion criteria were history of other neurological disorders, dyschromatopsia, uncorrected visual impairment, severe and disabling dyskinesia or tremor.

Table 2. Clinical data of the patients

Patients	UPDRS III (/108)				Motor improvement due to STN DBS only (%)	MMSE (/30)	MATTIS (/144)	BECK DEPRESSION INVENTORY (/63)
	STN DBS On		STN DBS Off					
	Med On	Med Off	Med On	Med Off				
1	4	5	8	14	64	30	144	1
2	5	11	19	39	72	29	143	7
3	12	17	37	38	55	29	139	20
4	6	16	24	37	57	28	142	6
5 ^β	20	24	30	55	56	25	136	8
6	15	22	28	29	24	28	140	6
7	10	19	23	41	54	29	138	18
8	5	5	23	28	82	30	143	6
9	3	10	28	58	83	29	138	4

10	8	13	21	30	57	29	134	12
11	6	13	16	23	43	29	144	8
12	3	5	17	28	82	28	141	7
13	2	8	16	17	53	29	139	10
14 ^β	8	19	21	32	41	29	134	5
15	8	8	58	70	89	30	144	20
16	2	3	7	13	77	26	137	17
mean	7 ^{*,‡}	12 ^{**}	24 ^{***}	35	62	29	140	10
range	2 - 20	3 - 24	7 - 58	13 - 70	24 - 89	25 - 30	132 - 144	1 - 20

BDI = Beck Depression Inventory; Mattis: Mattis scale; Med Off = Off medication condition; Med On = On medication condition; MMSE = Mini-Mental State Examination; UPDRS = Unified Parkinson's Disease Rating Scale.

*: p value between UPDRS III (STN DBS Off- Med Off) and (STN DBS On- Med On) = < 0.001

** : p value between UPDRS III (STN DBS Off- Med Off) and (STN DBS On- Med Off) = < 0.001

***: p value between UPDRS III (STN DBS Off- Med Off) and (STN DBS Off- Med On) = < 0.001

‡ : p value between UPDRS III (STN DBS On - Med Off) and (STN DBS On - Med On) = 0.01

^β: patients with one of the two global cognitive tests below the usual cut-off of cognitive impairment for PD patients. These 2 patients were however considered with no significant cognitive deterioration since the other test was in the normal range. These differences of results were interpreted as a consequence of low socio-educational level.

2.2. Task

The patients performed a common visual version of the Simon task in which they were to choose between a left- and a right-hand key press according to the color (green/red) of a visual stimulus presented a few degrees either to the left or the right of a central fixation point (Fig. 1). Performance, both in terms of error rates and mean reaction time, is better when the required response corresponds spatially to the irrelevant stimulus location (congruent association) than when it does not correspond (incongruent association). More details about the apparatus are available in Supplementary Doc.1.

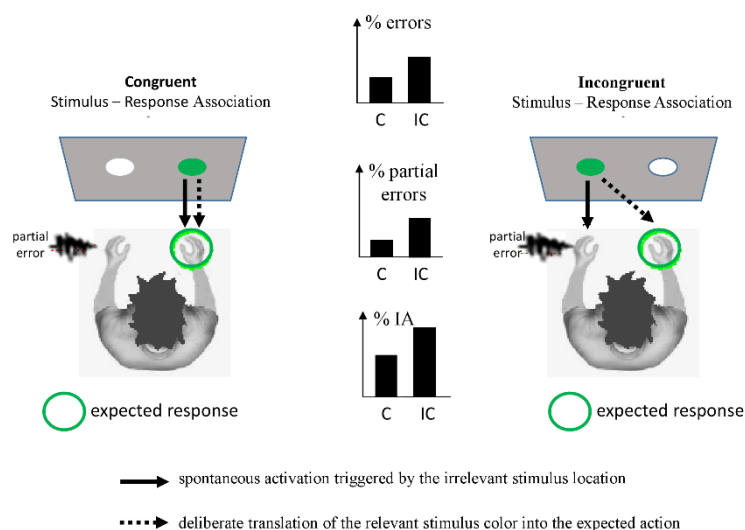


Figure 1. Simon task. Participants were instructed to press the left button in response to a red light and a right button in response to a green light (dashed line). Responses are also automatically driven by the irrelevant stimulus location, as indicated by the solid line. For congruent associations, both relevant (i.e. color) and irrelevant (i.e. location) stimulus attributes activate the correct action. On incongruent associations, the irrelevant attribute activates an incorrect response, which interferes with the implementation of the correct response. IA = Incorrect Activations; C = Congruent Condition; IC = Incongruent Condition.

2.3. Procedure and design

Each trial started with the blue fixation point lighting up. One second later, one of the two lateral bicolor diodes illuminated either in green or in red. The color and location of the stimuli were unpredictable. The patient was instructed to press the right or the left force sensor depending on the color of the stimulus as fast and as accurately as possible. The response extinguished the fixation point and the response signal, marking the end of the trial. If the response was not given within 1.5 s after stimulus onset, the trial ended the same way. The next trial started after 1.5 s. The trials were presented in blocks of 64, in which each type of stimulus was equiprobable. Each experimental session comprised of 6 blocks of 64 trials and lasted 20-25 min. Between blocks, the patient was provided with a few minutes of rest. The patients received an initial training session (one block of 64 trials) before being tested on four experimental sessions. The task was considered as correctly learned when few errors was made (<10%), and when patients were sufficiently relaxed to limit EMG noise. The four experimental sessions were spread over two days. Each day corresponded to the medication

status (On or Off). On each day, patients completed the experiment both On and Off DBS. The experiment thus included the four conditions of the full factorial design: Off Medication/Off DBS, Off Medication/On DBS, On Medication/Off DBS, On Medication/On DBS. A one hour break followed after switching DBS On or Off. The On Medication condition corresponded to the patient's regular medication intake (levodopa \pm dopaminergic agonists), and the experimental session was performed during the "best On" of each patient. The "best On" state refers to the moment where the motor clinical state of the patient was the best. It was generally between one and two hours after the regular dopaminergic treatment intake. The Off Medication condition was run after an overnight withdrawal of all dopaminergic treatment (for at least 12 hours). Color-response mapping instructions were counterbalanced across patients, as well as treatment modalities. Eight patients were instructed to press the left force sensor when the stimulus was green, and the right force sensor when the stimulus was red. The other 8 patients received the reverse mapping instructions. In each of these two groups, half of the patients started in the Off medication condition. Half of these patients performed the first experimental session On DBS, the second half started Off stimulation. The others performed the sessions in reverse order. Counterbalancing of DBS sessions was similar for the eight patients that started On medication.

2.4. Signal recordings and processing

The EMG activity of the flexor pollicis brevis was recorded bipolarly with surface Ag-AgCl electrodes, 6 mm in diameter, fixed about 10 mm apart on the skin of the thenar eminence. The EMG activity was amplified (gain 5000), the sampling rate was 1024 Hz (Filters: DC to 268 Hz, 3 dB/octave). The EMG signal was continuously monitored by the experimenter to prevent background activity in order to facilitate the EMG onset detection. If

the signal became noisy due to tonic muscle activity, the experimenter immediately asked the patient to relax his (her) hand muscles.

The recorded EMG signals were first off-line high-pass filtered at 10 Hz and then inspected visually. The EMG onsets were hand scored because human pattern recognition processes are superior to automated algorithms. Although automated algorithms can be useful (e.g., Hodges and Bui, 1996; Van Boxtel et al., 1993) the ultimate standard, against which the accuracy of the different algorithms is rated, remains visual inspection (see Staude et al., 2001). To overcome subjective influence on the scoring, the experimenter who processed the signals was blind to the type of associations (congruent, incongruent), medication status (On, Off) or DBS status (On, Off) to which the traces corresponded.

2.5. Data analysis

Besides mean RT and error rate, we also performed distribution analyzes of those variables for comparison with data in the literature (Wylie et al. 2010). Reaction Time for correct responses were vincentized in 7 bins (Ratcliff, 1978) and the differences between incongruent and congruent trials was computed for each bin. These differences were plotted as a function of the mean reaction time of each bin. Distribution analysis for accuracy (the so-called “Conditional Accuracy Functions”) are constructed with the same logic, with the following differences: both correct and erroneous trails are vincentized together in 7 bins, and for each bin, the proportion of correct response is computed.

Besides mean reaction time, additional chronometric variables extracted from EMG were analyzed in the present study; they are illustrated in Fig. 2. Reaction time was measured from stimulus onset to the mechanical response. It was fractionated into two sub-intervals: from stimulus to EMG onset (pre-motor time) and between EMG onset and mechanical response defined at the force threshold crossing (motor time).

Recording EMG in such tasks reveals partial EMG errors, that are small bursts of EMG activity in the incorrect response effector preceding that of the correct response effector. Importantly, to be differentiated from a tonic activity and to be classified as a partial EMG error, the EMG signal deflection was to be phasic and return to baseline (rest) level before the onset of the response-related EMG activity in the correct hand.

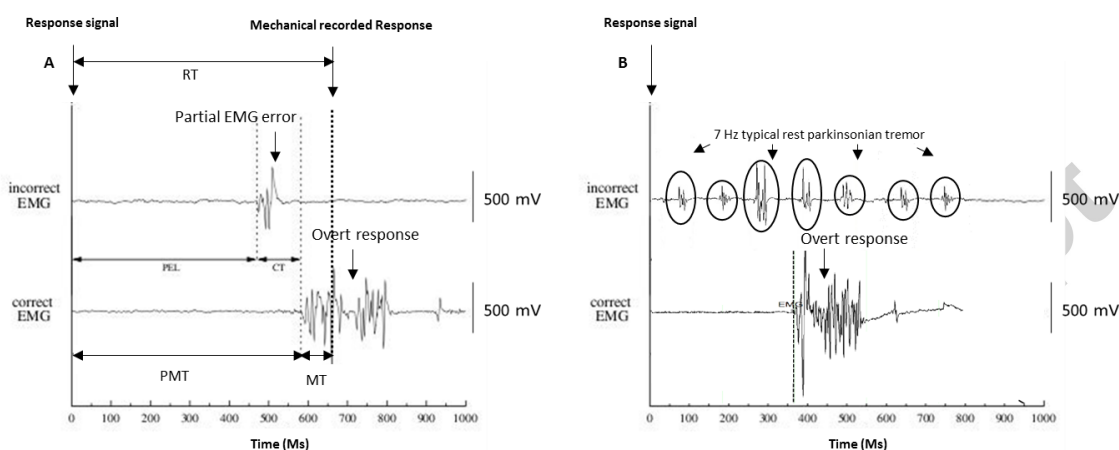


Figure 2. EMG records and chronometric measures. *A:* Traces recorded during a partial EMG error trial showing the electromyographic activity of the agonists of the two responses as a function of time (in ms) from stimulus onset (time 0). Lower trace: correct activity. Upper trace: incorrect activity. RT = reaction time (from stimulus onset to the correct mechanical recorded response); PMT = Premotor Time (from stimulus onset to EMG onset in the muscle involved in the correct response); MT = Motor Time (from EMG onset in the muscle involved in the correct response to the correct mechanical recorded response); PEL = partial EMG error latency (from stimulus onset to EMG onset, if any, in the muscle involved in the incorrect response); CT = correction time (from EMG onset in the muscle involved in the incorrect response to EMG onset in the muscle involved in the correct response). In contrast to tremor which causes tonic rhythmic pulses, partial EMG errors consist of single phasic bursts. *B:* Example of a trial discarded because of intercurrent muscle twitches due to tremor on the upper trace (within ellipses). The lower trace displays the EMG activity involved in a response. Note that discarded trials were rare (2,91 %), which is compatible with clinical observations that tremor and dystonia disappear when PD patients engage in a task.

Besides counting their occurrence, several additional variables can be extracted from these partial EMG errors. The correction time is defined as the interval separating partial EMG error onset from the EMG activity involved in the required response. The Correction Ratio is defined as:

$$\text{Correction Ratio} = N_{pe} / (N_{pe} + N_{er})$$

where N_{pe} reflects the number of partial EMG errors and N_{er} the number of overt errors. In other words, the Correction Ratio reflects the number of corrected incorrect activations divided by the overall number of incorrect activations (corrected or not).

In order to assess the dynamics of impulse expression, distribution analysis was also applied to EMG activities. All EMG activities, both correct and incorrect ones, and the one leading to partial or overt errors were put together and vincentized. For each bin the proportion of correct activations was computed (see Ramdani et al., 2015). This provides the probability that the first EMG activity occurs on the correct hand, as a function of the latency of this EMG activity, irrespective of a possible subsequent correction. They will be termed EMG-CAF in the following. Functionally speaking, they reflect the temporal dynamics of impulse expression at the muscular level, irrespective of the successful suppression of erroneous impulses in partial EMG error trials.

The ANOVAs reported in the next section involved Congruency of the stimulus-response association (congruent, incongruent), STN DBS (On, Off), and Medication (On, Off) as within-subject variables. For the Conditional Accuracy Functions and EMG-Conditional Accuracy Functions analyses, the Bin (1-7) was added as a fourth factor in the ANOVA. Proportions (errors, partial EMG errors, incorrect activations rates, Correction Ratio) were subjected to arcsine transformation so as to stabilize their variance before being submitted ANOVAs (see Winer, 1971, p. 221). However, even if this transformation improves normality of the data, normality can still be violated, especially in the case of CAFs where many cells of the design saturate at 1 (especially for higher bins). Although ANOVA is known to be very robust to normality assumption, we complemented all the necessary analyses by permutation tests (N permutations = 1000, with the 'ez' package, version 4.4.0, R version 3.2.3, running on linux). The associated p values will be reported in parenthesis after

the canonical ANOVA. Effect sizes were estimated by the generalized eta square (η^2_G , Olejnik & Algina, 2003) as it is best suited for within-participant designs (Bakeman, 2005). In case of sphericity assumption violation, degrees of freedom were therefore corrected using Huynh-feldt estimates of sphericity (ϵ) (Huynh & Feldt, 1976); ϵ and p-value after correction are reported for significant effect.

3. Results

We will first present the results obtained based on common behavioral measures of performance on the Simon task: mean reaction time, accuracy rate, and Conditional Accuracy Functions. Second, we will present the EMG results. This “EMG augmented analysis” includes both frequency data (proportion of different types of trials and Correction Ratio) and chronometric data (pre-motor time, motor time, partial error latencies and correction time).

Omissions were low and occurred on 0.89% of the trials and were discarded from further analysis.

3.1. Classical behavioral measures

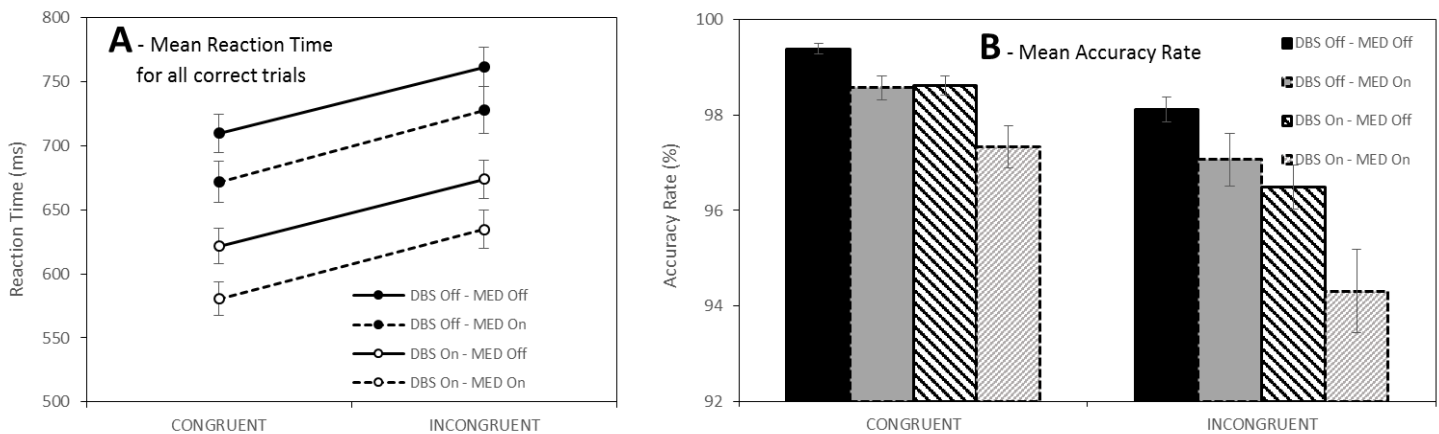


Figure 3: Classical behavioral measures. **A:** Mean Reaction Time (ms, ordinate) of all the correct responses in the four conditions as a function of the type of Stimulus - Response Association (Congruent versus Incongruent, Abscissa). Vertical bars indicate SEs. (black circles: DBS Off, white circles: DBS On / solid line: Medication Off, dashed line: Medication On). **B:** Mean accuracy rate (% , ordinate) in the four conditions as a function of Stimulus - Response Association (Congruent versus Incongruent, Abscissa). Vertical bars indicate SEs.

3.1.1. Mean Reaction Time for all correct trials.

The results are presented in Fig. 3A. Mean reaction time was shorter for congruent (648 ms) than for incongruent (699 ms) associations, $F(1,15) = 79.61$, $p < 0.001$, $\eta^2 = 0.03$. Mean reaction time was shorter when DBS was On (628 ms) than when it was Off (718 ms), $F(1,15) = 13.45$, $p < 0.001$, $\eta^2 = 0.07$, and when patients were On medication (654 ms) than when they were Off medication (692 ms), $F(1,15) = 7.73$, $p < 0.01$, $\eta^2 = 0.01$. There was no significant interaction between any of the factors, with all $F_s < 1$.

3.1.2. Accuracy.

The results are presented in Fig. 3B. Accuracy rate of overt responses was higher for congruent (98.49%) than for incongruent (96.50%) associations, $F(1,15) = 11.91$, $p < 0.001$, $\eta^2 = 0.07$, (permutation analysis, $p < 0.01$). It was lower when DBS was On (96.69%) than when it was Off (98.29%), $F(1,15) = 6.85$, $p = 0.02$, $\eta^2 = 0.05$ (permutation analysis, $p = 0.01$) and tended to be lower when medication was On (96.83%) than when it was Off (98.16%), $F(1,15) = 3.38$, $p = 0.09$, $\eta^2 = 0.03$ (permutation analysis, $p = 0.04$). Since the direction of this effect was expected on the basis of Fluchère et al. (2015), it was assessed using a one-sided, two-paired Student's t test. This comparison reached significance, $t(15) = 1.95$; $p < 0.05$, replicating the results of Fluchère et al. (2015). Finally, there was a marginally significant interaction between Congruency and STN DBS, suggesting that the effect of STN DBS tends to be larger for incongruent than for congruent associations, $F(1,15) = 4.1$, $p = 0.06$, $\eta^2 = 0.01$ (permutation analysis, $p = 0.03$). No other interaction between any of the factors approached significance, with lowest p -value = 0.26 (permutation analysis, lowest p -value = 0.24).

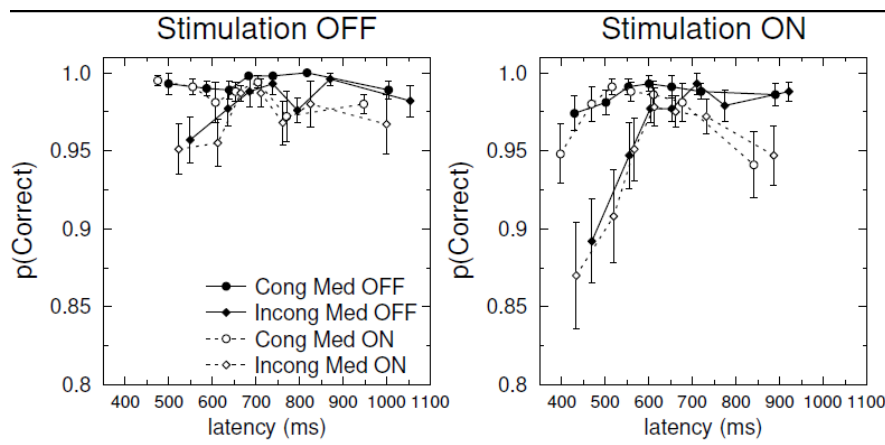


Figure 4: Conditional Accuracy Functions. The accuracy rate (in ordinate) is represented as a function of reaction time (in abscissa, ms), with STN DBS Off (left panel) and STN DBS On (right panel). Vertical bars indicate SEs. Cong = Congruent association; Incong = Incongruent association.

3.1.3. Conditional Accuracy Functions.

Examination of Fig. 4 suggests that the effect of congruency on overt response accuracy is not homogeneous as a function of reaction time. This pattern was assessed by adding the factor “Bin” into the ANOVA and evaluating the interactions terms. The difference in accuracy between incongruent and congruent associations was more pronounced for the fastest responses and vanished as response latency increased: interaction Bin x Congruency: $F(6,90) = 11.43$, $\epsilon = 0.51$, $p < 0.001$, $\eta^2 = 0.04$, permutation analysis, $p < 0.01$). This interaction was modulated by STN DBS (interaction Bin x DBS STN x Congruency: $F(6,90) = 3.79$, $\epsilon = 0.44$, $p = 0.02$, $\eta^2 = 0.01$, permutation analysis, $p = 0.03$). The drop in accuracy for fast responses was much larger for the incongruent associations when DBS was On replicating the finding of Wylie et al. (2010, Fig. 3). All other interactions between any of the factors did not reach significance level, with lowest p-value = 0.20 (permutation analysis, lowest p-value = 0.22).

3.1.4. Delta-plots analyses.

Besides Conditional Accuracy Functions, Wylie et al. (2010) also analyzed the dynamics of the interference effect as a function of reaction time duration. This is done by computing the size of the Simon effect on RT for each bin, and plotting these values as a function of the mean reaction time of the Bin (see Supplementary Fig. 1). It is common practice to compute the slopes of those delta plots and enter them in the ANOVA. As in Wylie et al. (2010), we entered 7 bins into the analysis. The ANOVA on the slope including Medication, STN DBS and Bin only revealed a marginal interaction between STN DBS and Bin ($F(5,75) = 2.16$, $\epsilon = 1.08$, $p = 0.07$, $\eta^2 = 0.02$), indicating that the last slope tended to be more negative when DBS is On, in agreement with the data of Wylie et al. (2010). Overall, on overt behavioral data, the present data replicate Wylie et al. (2010). We can hence proceed to EMG analysis.

3.2. EMG augmented measures

Due to tonic activity, tremor, and EMG bursts recorded from response agonist preceding the contraction involved in the response, 2.91% of the trials were discarded from the analyses (an example of a discarded trial is provided in Fig. 2B).

3.2.1. Pure Correct Trials

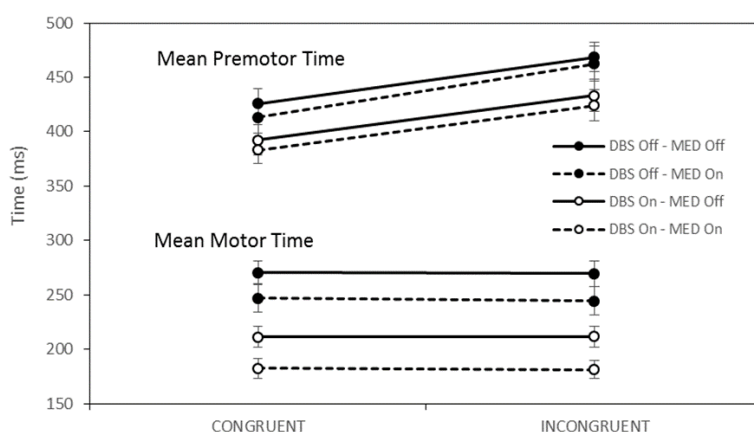


Figure 5: Reaction Time Fractioning: Mean Premotor and Motor Time. Latencies (ms, ordinate): Mean Premotor Time (top) and Mean Motor Time (bottom) in the four condition as a function of the type of Stimulus - Response Association (Congruent versus Incongruent, Abscissa). Vertical bars indicate SEs. (black circles: DBS Off, white circles symbols: DBS On / solid line: Medication Off, dashed line: Medication On).

3.2.1.1. Motor Time.

Motor time was not influenced by the type of stimulus-response association, $F(1,15) < 1$. Both STN DBS (On: 197 ms, Off: 258 ms, $F(1,15) = 16.82$, $p < 0.001$, $\eta^2 = 0.12$) and Medication (On: 214 ms, Off: 241 ms, $F(1,15) = 24.4$, $p < 0.001$, $\eta^2 = 0.03$) shortened motor time. The two effects were additive as there was no significant interaction between any of the factors, with all $F_s < 1$ (Fig. 5).

3.2.1.2. Premotor Time.

Pre-motor time was shorter for congruent (404 ms) than for incongruent (447 ms) associations, $F(1,15) = 63.30$, $p < 0.001$, $\eta^2 = 0.04$, and when STN DBS was On (408 ms) than when it was Off (443 ms), $F(1,15) = 5.50$, $p = 0.03$, $\eta^2 = 0.02$. In contrast, pre-motor time was not affected by Medication, $F(1,15) < 1$. There was no significant interaction between any of the

factors, with all $F_s < 1$ (Fig. 5). The effect of medication on reaction time hence exclusively affected the motor time.

3.2.2. Incorrect Activation Trials (overt and partial EMG errors)

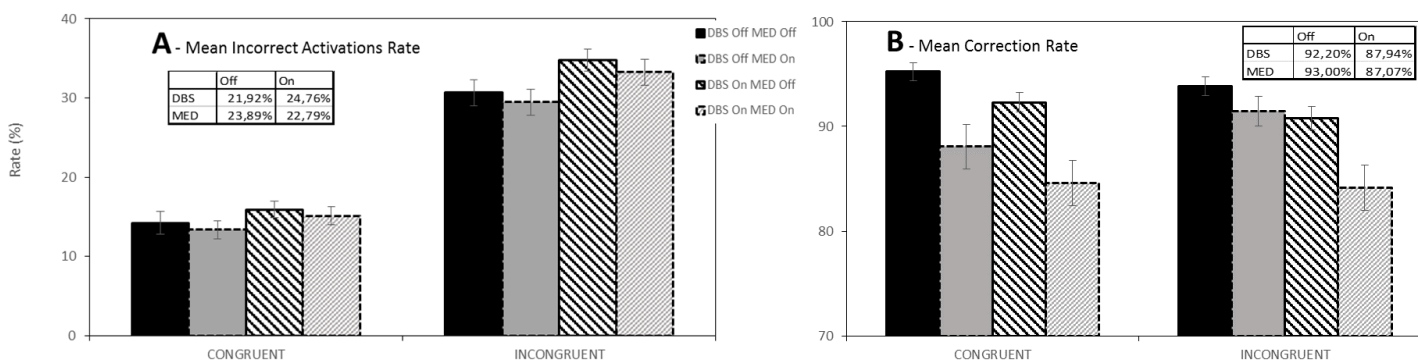


Figure 6: Mean Incorrect Activation Rate and Correction Ratio. A: Percentage (% , ordinate) of all incorrect activations in the four conditions as a function of the type of Stimulus - Response Association (Congruent versus Incongruent, Abscissa). Vertical bars indicate SEs. **B:** Correction ratio (% , ordinate) in the four conditions as a function of the type of Stimulus - Response Association (Congruent versus Incongruent, Abscissa). Vertical bars indicate SEs. Tables indicate mean values for each of these rates as a function of STN DBS state (upper row) and as a function of medication state (lower row). There was no interaction between STN DBS and dopaminergic treatment.

3.2.2.1. Incorrect Activation Rate.

Incorrect activations were more frequent for incongruent (32.03%) than for congruent trials (14.65%), $F(1,15) = 85.91$, $p < 0.001$, $\eta^2 = 0.39$ (permutation analysis, $p < 0.01$). Incorrect activations also tended to be more frequent when DBS was On (24.76%) than when it was Off (21.92%), $F(1,15) = 3.64$, $p = 0.08$, $\eta^2 = 0.02$ (permutation analysis, $p = 0.06$). There was no effect of Medication, $F < 1$ (permutation analysis, $p = 0.71$). There was no significant interaction between any of the factors, with lowest p-value = 0.12 (permutation analysis, lowest p-value = 0.07) (Fig. 6A).

3.2.2.2. Correction Ratio.

There was no main effect of Congruency, $F(1,15) < 1$. Correction Ratio was reduced when DBS was On (87.94%) than it was Off (92.17%), $F(1,15) = 7.88$, $p = 0.01$, $\eta^2 = 0.03$ (permutation analysis, $p < 0.01$), and when the patients were taking their medication (87.07%)

than after withdrawal (93.04%), $F(1,15) = 7.35$, $p = 0.02$, $\eta^2 = 0.06$ (permutation analysis, $p = 0.03$). There was no significant interaction between any of the factors, with lowest p -value = 0.19 (permutation analysis, lowest p -value = 0.39) (Fig. 6B).

3.2.2.3. *Partial error latency and correction time.*

Results are available in the supplementary doc. 2.

3.2.2.4: *EMG-Conditional Accuracy Functions.*

The EMG-Conditional Accuracy Functions plotted in Fig. 7 seem very similar across STN DBS and Medication conditions, suggesting that neither factors affect them, in clear contrast with Fig. 4 where STN DBS increased fastest incongruent overt errors. Statistical analysis confirmed this impression. The Congruency effect was large for the fastest responses and progressively vanished as the latency of the activation increased, $F(6,90) = 41.22$, $\epsilon = 0.36$, $p < 0.001$, $\eta^2 = 0.20$ (permutation analysis, $p < 0.01$). No significant interaction between the factor Bin and any of other factors reached significance level, all $F_s < 1$ (permutation analysis, lowest, p -value= 0.13).

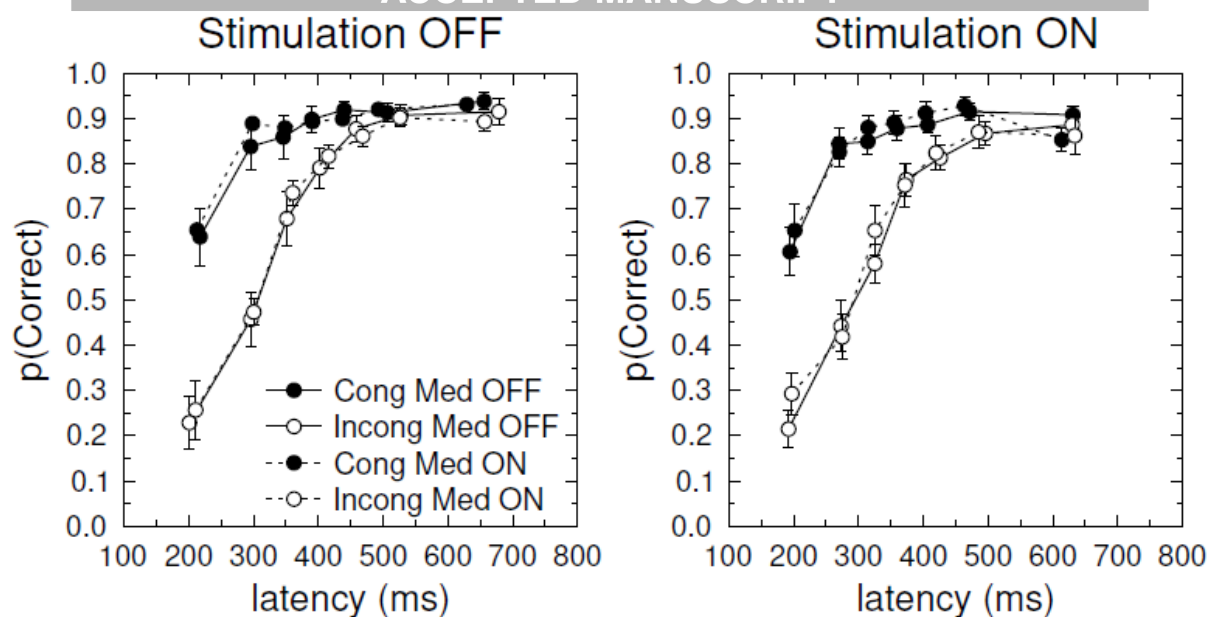


Figure 7: EMG – Conditional Accuracy Functions. The proportion of pure correct activations (in ordinate) is represented as a function of the premotor time (in abscissa, ms) when STN DBS is Off (left panel) and when STN DBS is On (right panel). Incorrect activations are associated with the shortest latencies on incongruent associations. Vertical bars indicate SEs. Cong = Congruent association; Incong = Incongruent association.

4. DISCUSSION

The aim of the present study was to assess the effects of STN DBS and the interaction with dopaminergic medication on action impulsivity in PD patients. By analyzing EMG activity during performance on the Simon task that requires overriding erroneous response tendencies, we could assess these effects on two components of action impulsivity (DeYoung, 2011) otherwise indissociable: expression and suppression of subthreshold impulsive errors. In what follows, we first comment the results obtained by traditional analyses of behavioral data. We then discuss how our augmented EMG measures help understand 1) the interpretation of traditional behavioral data, 2) the nature of the impulsivity observed in PD patients, and 3) basal ganglia functions in action selection and control, and on their modeling.

4.1. Traditional behavioral measures

It is relevant to note that in PD patients, whatever STN DBS or medication condition, the behavioral results classically reported in healthy participants were replicated. First, performance, expressed both in terms of accuracy rate and reaction time, was better for

congruent than for incongruent stimulus-response associations. This indicates that in PD patients, like in healthy subjects, the irrelevant spatial correspondence between the stimulus location and the response location interferes with voluntary action control (Wylie et al., 2010). Second, both STN DBS and dopaminergic treatment induced a speed-accuracy tradeoff. PD patients reacted faster and committed more overt errors when STN DBS was On than when it was Off, thereby replicating several previous clinical studies (Hershey et al., 2004; Williams et al., 2005, van den Wildenberg et al., 2006; Wylie et al., 2010). Patients also reacted faster and made more errors when they were On than when they were Off their usual dopaminergic treatment, thus replicating the data reported by Fluchère et al. (2015). In terms of the models by Frank et al. (2007) and Wiecki and Frank (2013), this is in line with the notion that both treatments reduce the STN outputs to the thalamus, lowering the response threshold formalized in the drift diffusion model (Ratcliff et al., 1978) and allowing fast impulsive erroneous responses to occur. This interpretation further satisfactorily accounts for the behavioral effects of STN DBS on performance in a stop-signal task reported by Obeso et al. (2014). We must acknowledge that with respect to dopaminergic medication, this interpretation should be further documented since the only evidence comes from the present study and from a previous study of our group (Fluchère et al., 2015; but also Wylie et al., 2012).

Importantly, as demonstrated by Wylie et al. (2010), the speed-accuracy tradeoff induced by STN DBS was not homogeneously distributed over time: STN DBS specifically increased the occurrence of fast overt errors for incongruent associations. According to the authors, fast response errors reflect the capture of the motor system by involuntary action impulses, a capture reflected in the ratio between correct and erroneous fast responses. Since for incongruent associations, STN DBS increased the occurrence of fast error responses, Wylie et al. concluded that stimulation increases the capture of the patients' motor system by

impulses triggered by the irrelevant stimulus location, hence leading to more impulsive fast errors for incongruent associations. This interpretation only holds if the amount of fast errors is solely driven by the strength of the response capture. Recent EMG data, however, suggests that it might also be affected by corrective processes (see e.g. Spieser et al., 2015). Such an interpretation is further contradicted by the observation that many correct response trials contain subthreshold muscle activity in the incorrect hand, a so called partial EMG error (Hasbroucq et al., 1999; Burle et al., 2002). Indeed, while reflecting impulsive response capture, such partial EMG errors have been suppressed before being behaviorally committed. Hence, an increase in the frequency of fast overt errors may also be due to a reduced capacity to correct impulsive response capture (see Spieser et al., 2015 for related matter). Note that Wiecki and Frank's (2013) model and all its formal cognates (e.g., Ratcliff & Smith, 2004, Hubner et al., 2010, White et al., 2011) do assume that motor activity is engaged in an all-or-none fashion once the decision threshold is reached, an assumption contradicted by the mere occurrence of partial errors.

Medication also induced a speed-accuracy tradeoff. In contrast to that of STN DBS, this effect seemed to be homogeneously distributed: accuracy was lowered by this treatment irrespective of reaction time. This speed-accuracy is not attributable to an increase of fast errors for incongruent associations and cannot therefore be interpreted in terms of increased response capture (Ridderinkhof, 2002).

4.2. Augmented measures with EMG

Recording EMG activity in patients first allowed to fractionate the global reaction time into two intervals: from stimulus onset to EMG onset (pre-motor time) and from EMG onset to mechanical response (motor time). This fractioning proved useful to clarify the impact of the two treatments on action control. Indeed, both STN DBS and medication shortened reaction time. Based on behavioral observation, one may conclude that the effect of

the two treatments on the underlying response processes are similar. Reaction time fractioning provides a very different picture: while DBS affected both pre-motor time and motor time (replicating results of Kumru et al (2003)), medication specifically affected motor time, leaving pre-motor time unaffected. Hence, EMG analysis allows to differentiate effects that are apparently similar on overt behavior. It is interesting to note that in healthy subjects, levodopa shortens not only pre-motor time (Rihet et al., 2002) but also motor time (Hasbroucq et al., 2003).

The EMG activity of the patients further led us to distinguish three trial categories: full overt errors, partial EMG errors, and correct responses. As for healthy subjects, incorrect activations were more frequent for incongruent than for congruent associations, thereby directly reflecting response capture or, in other words, the EMG expression of impulses triggered by the irrelevant stimulus location (Hasbroucq et al., 2009). As in healthy participants this effect was not homogeneously distributed over time (see van den Wildenberg et al., 2010 for an overview). Congruency essentially affected the fastest incorrect activations and its influence vanished as the latency of incorrect activations increased. This temporal dynamics shows that early during the reaction time interval, for incongruent associations, the irrelevant stimulus location activates the non-required response (Ridderinkhof, 2002) and on a proportion of trials, this rapid activation results in quantifiable muscle contractions (Hasbroucq et al., 1999; van den Wildenberg et al., 2010). Later during the reaction time interval, the activation of the required response replaces this initial incorrect activation and this process is reflected by a diminution of the frequency of incorrect activations for incongruent trials.

Neither STN DBS nor medication significantly affected the frequency of incorrect activations, suggesting that impulse expression or response capture is little affected by these treatments. There was a non-significant trend for STN DBS to increase the number of

incorrect activations. Importantly, this trend was present for both congruent and incongruent trials and examination of the EMG-Conditional Accuracy Functions further revealed that this trend was consistent across the entire reaction time distribution. Such a pattern suggests that this increase is not indexing a stronger response capture, but more likely an increased motor noise. The increase in fast overt errors for incongruent associations caused by STN DBS seems therefore essentially due to impaired impulse correction. This interpretation was confirmed by analysing the correction ratio, which is the ratio between the number of partial EMG errors and the total number of incorrect activations. Both medication and STN DBS decreased the correction ratio, demonstrating that the two treatments impair the patients' ability to suppress impulses before they provoke overt errors. Congruency interacted neither with medication nor with STN DBS, which suggests that the impairment is relative to both internally and externally triggered impulses and is therefore not related to impulse capture. The only measurable effect of medication on impulsivity is hence attributable to impaired impulse suppression. Similarly, the major effect of STN DBS on action impulsivity seems linked to reduced impulse suppression rather than to increased impulse expression or response capture. This conclusion may seem at odd with that of Wylie et al. (2010). Indeed, based on distribution analysis of overt behavior that indicated reduced interference for slower responses, they concluded that STN DBS would improve rather than impair impulse suppression. It is important to note that this discrepancy is not due to incompatible results: the present reaction time data do replicate the patterns reported by Wylie et al. (see our Fig. 4 and 5, and Fig. 3 and 4 of Wylie et al). The interpretation differences stem from the different markers used. Following the propositions of Ridderinkhof (2002), Wylie et al. used the shape of the delta-plots (see Fig. 5) to infer the strength of the suppression. Although some arguments exist for a link between the delta-plots shape and incorrect response suppression (e.g. Forstmann et al., 2008), delta-plots are at best a proxy for the suppression mechanism. In

contrast, here we used a more direct measure of incorrect response correction, through the correction ratio and the comparison between Conditional Accuracy Functions and EMG-Conditional Accuracy Functions. The presence of partial errors and negative-going delta-plot slopes have been linked empirically (Burle et al., 2002, 2014), but the exact nature of this link still need to be clarified theoretically. Recent modelling work suggests that the shape of the delta-plots is linked to the strength and duration of the automatic response capture (Ulrich et al., 2015), but one still need to formalize the triadic link between response capture, partial errors, and delta-plots (see Servant et al., 2016 for an attempt).

While that both dopaminergic Medication and STN DBS modify the processes implemented through the indirect pathway of the basal ganglia and have synergistic influences, evidence suggests that the two treatments may affect different subfunctions. Dopamine seems involved in the processing of positive and negative decision outcomes and STN DBS would alter ability to solve response conflict (Frank et al, 2007; Jahanshahi et al, 2015). In the present study, the additive effects of the two treatments on the chronometric variables may support this interpretation. However, correction ratio analysis revealed that both medication and STN DBS impair impulse suppression, thereby demonstrating that the two treatments have a common functional locus despite their additive effects.

As a matter of fact, current interpretations of additive effects rely on a rule of a thumb consisting in reversing the logical premise according to which “if two manipulations selectively influence two different process, they will have additive effects” into: “if two manipulations display additive effects then each manipulation affect a different processes”. The present results illustrate the hazard of reversing the original logical premise when interpreting the joint effects of two manipulations (see Pieters, 1983).

4.3. Relation to drift diffusion models

Formal models of decision making in relation with basal ganglia functioning (Wiecki & Frank, 2013) have suggested that STN DBS lowers the response threshold, hence inducing a speed-accuracy trade-off. Such models, based on the standard “drift diffusion model”, cannot account for the dynamics observed during conflict tasks (Hübner et al., 2010, White et al., 2011, Ulrich et al., 2015), nor for the presence of partial errors (Servant et al., 2015). To account for partial errors, Servant et al. (2015) introduced the notion of two thresholds: one to trigger EMG activity, and one for the mechanical, overt, response. Owing Servant et al. (2015), the pre-motor and the incorrect activations rate reflect the level of the first threshold (called EMG-threshold), whereas motor reflect the level of the second one (called “mechanical threshold”). The interval between the two thresholds allows for correction to occur. How to interpret the present results within this framework? In agreement with Wiecki & Frank (2013), both STN DBS and medication lower the mechanical threshold (shorter reaction times). However, while medication does not seem to affect the EMG-threshold (similar pre-motor times and incorrect activations rates), STN DBS also lowers this threshold (shorter pre-motor times and slightly increased incorrect activations rate). The effect of STN DBS on EMG-threshold may seem at odd with the similar EMG-Conditional Accuracy Functions depicted on Fig. 4. However, patients tended to make more incorrect activations when STN DBS was on, but this effect was not modulated by congruency. Furthermore, the effect of STN DBS on pre-motor time was small. Hence, the impact of this lowering was likely tiny, making it less reliable, and it affected the whole distribution, irrespective of time, of both congruent and incongruent trials. The lesser effect of STN DBS on the “EMG-threshold” in comparison with its effect on the “mechanical threshold” is responsible of a reduction of the distance between these two thresholds, leaving less time for correction to occur. This explains that STN DBS impairs suppression process as it has less time to occur.

Recent neurophysiological data support the notion that STN plays a key role in regulating response threshold. Herz et al have shown that the modulation of oscillatory activities in the low frequency and beta range within the STN correlate with speed-accuracy adjustments (Herz et al, 2017). More precisely, increases of STN low frequency oscillations signal seem to increase response threshold while cue-induced reductions of STN beta power signal decreased it (irrespective of instructions). Each of these oscillations were phase-locked with different cortical regions activity: STN Low frequency oscillations coupled with the Prefrontal cortex (i.e. to the hyper direct pathway) whereas STN beta power was linked to the motor cortex (i.e. to the indirect pathway). Besides, both STN DBS and dopamine are known to reduce beta oscillations in the STN (Eusebio et al, 2011). From these results, the present data allow us to conjecture that decreased Beta power induced by both STN DBS and dopaminergic treatment could explain the lowering of the overt response threshold via their action on the indirect pathway. In addition, by superimposing a highly organized activity, STN DBS might further prevent the up modulation of low frequency oscillations thereby lowering EMG-thresholds.

In conclusion, although STN DBS and dopaminergic treatment dramatically improve motor symptoms in PD, our study shows that these therapeutics play a negative role on performance in terms of accuracy. By operationalizing the two components of impulsivity as defined by DeYoung (2011), we were able to dissociate the effect of STN DBS and dopaminergic treatment on impulses' activation and suppression in PD, without relying on the model of Ridderinkhof. STN DBS impairs the patient's capacity to suppress ongoing but erroneous action tendencies and caused the muscular expression of fast incorrect impulses. Dopaminergic treatment only impairs the capacity to suppress incorrect impulses, without interfering with the STN DBS effect. The overall pattern of results hence fit with the notion

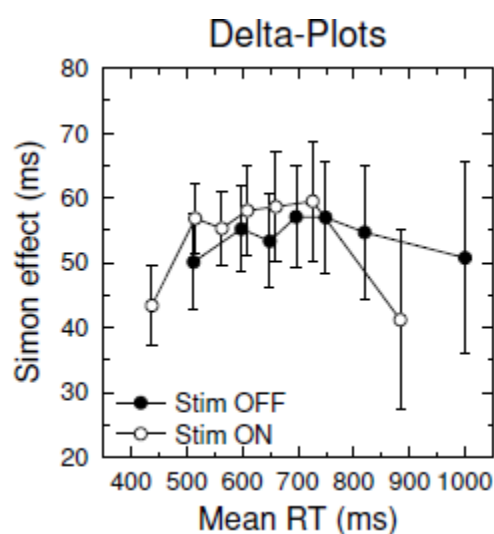
that both medication and STN DBS affect the mechanical threshold (see Wiecki & Frank, 2013), but that only STN DBS lowers the EMG-threshold.

Funding:

The present work was supported by an AORC grant from Assistance Publique-Hôpitaux de Marseille to Frédérique Fluchère. Boris Burle is supported by a European Research Council under the European Community's Seventh Framework Programme (FP7/2007-2013 Grant Agreement no. 241077)

Supplementary Material

Supplementary Fig.1: Delta-plots analysis



The Simon effect (in ordinate, ms), defined by the RT difference between incongruent and congruent trials) is represented as a function of RT (in abscissa, ms), and STN DBS status (On or Off). Vertical bars indicate SEs.

Supplementary Doc.1: Details about apparatus and stimuli

Seated in an armchair, the patient faced a black plastic board on which the stimuli were presented. A blue light-emitting diode fixed on the center of the display served as a fixation point. The stimuli were presented by two bicolor (red/green) light-emitting diodes located on the left and right of the fixation point, the distance between these light-emitting diodes subtended 3.2° of visual angle. When one of the lateral light-emitting diodes was lit, the association was either congruent or incongruent, depending on whether the correct response hand was on the same side or on the opposite side as the signal. A pull-out plastic table (100 x 50 cm) was placed in front of the subject. Two plastic cylinders (3 cm in diameter, 10 cm in

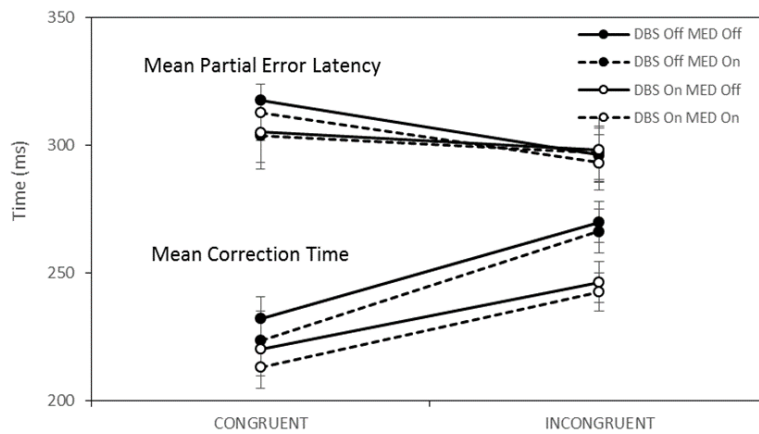
height) serving as handgrips were fixed 32 cm apart on the table and 16 cm on the left and right of the subject's midsagittal plane. A force sensor (Model 1042, Tedeo-Huntleigh, Cardiff UK) was fixed on the top of each cylinder. The patient was to keep the distal phalanxes of his thumbs on the sensors. The response (correct or incorrect) was an isometric press of 8 N on one of the two sensors according to the color of the stimulus. One patient had difficulties reaching this force threshold in the DBS Off- Med Off condition, leading to a large number of apparent "omissions". However, the EMG pattern of this patient was overall comparable to all the other ones. We hence decided to offline recompute behavioral measures as if the force threshold had been lower. Importantly, the same new threshold (5N) was applied to all the conditions (Medication and DBS On and Off), so that the within-patient comparisons remain perfectly valid and comparable to the other patients. The value of the threshold was chosen so that the overall number of overt errors was in the same range as the other patients.

Supplementary Doc.2: Other EMG-augmented measures

1- Partial error latency. There was neither an effect of Congruency, $F(1,15) = 2.96$, nor of Stimulation, $F(1,15) < 1$, nor of Medication, $F(1,15) < 1$. There was no significant interaction between any of the factors, with lowest p-value = 0.23 (Supplementary Fig. 2).

2- Correction Time. Correction time was shorter for congruent (222 ms) than for incongruent (256 ms) trials, $F(1,15) = 15.85$, $p < 0.001$, replicating previous results in healthy participants (Burle et al., 2002). It was also shorter when DBS was On (231 ms) than it was Off (246 ms), $F(1,15) = 5.36$, $p = 0.04$, . There was no main effect of Medication, $F(1,15) < 1$. There was no significant interaction between any of the factors, with lowest p-value = 0.28 (Supplementary Fig. 2).

Supplementary Figure 2



Mean Partial Error Latency and Mean Correction Time

Latencies (ms, ordinate): Mean Partial Error Latency (on the top) and Mean Correction Time (on the bottom) in the four condition as a function of the type of Stimulus - Response Association (Congruent versus Incongruent, Abscissa). Vertical bars indicate SEs. (black circles: DBS Off, white circles: DBS On / full line: Medication Off, dotted line: Medication On).

Accepted manuscript

References

- Ballanger B**, van Eimeren T, Moro E, Lozano AM, Hamani C, Boulinguez P, et al. Stimulation of the subthalamic nucleus and impulsivity: Release your horses. *Annals Neurol*. 2009;66:817–24.
- Bakeman, R.** (2005). Recommended effect size statistics for repeated measures designs. *Behavior Research Methods*, 37 (3), 379-384.
- Burle B**, Possamaï CA, Vidal F, Bonnet M, Hasbroucq T. Executive control in the Simon effect: an electromyographic and distributional analysis. *Psychol Res*. 2002;66:324-36.
- Burle B**, Roger C, Allain S, Vidal F, Hasbroucq T. Error negativity does not reflect conflict: a reappraisal of conflict monitoring and anterior cingulate cortex activity. *J Cogn Neurosci*. 2008;20:1637-55.
- Burle B**, Spieser L, Servant M, Hasbroucq T. Distributional reaction time properties in the Eriksen task: marked differences or hidden similarities with the Simon task? *Psychon Bull Rev*. 2014;21:1003-10.
- Christenson GA**, Faber RJ, de Zwaan M. Compulsive buying: descriptive characteristics and psychiatric comorbidity. *J Clin Psychiat*. 1994;55: 5-11.
- DeYoung CG**. Impulsivity as a personality trait. 2011. In KD Vohs and RF Baumeister, (Eds.), *Handbook of self-regulation: research, theory, and applications* (pp 485-504). New-York: Guilford Press.
- Eusebio A**, Thevathasan W, Doyle Gaynor L, Pogosyan A, Bye E, Foltynie T, Zrinzo L, Ashkan K, Aziz T, Brown P. Deep brain stimulation can suppress pathological synchronisation in parkinsonian patients. *J Neurol Neurosurg Psychiatry*. 2011 May;82(5):569-73.

Fluchere F, Witjas T, Eusebio A, Bruder N, Giorgi R, Leveque M, Peragut JC, Azulay JP, Regis J. Controlled general anaesthesia for subthalamic nucleus stimulation in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2014;85(10):1167-73.

Fluchère F, Deveaux M, Burle B, Vidal F, van den Wildenberg WP, Witjas T, Eusebio A, Azulay JP, Hasbroucq T. Dopa therapy and action impulsivity: subthreshold error activation and suppression in Parkinson's disease. *Psychopharmacology*. 2015;232(10):1735-46.

Forstmann B U, Jahfari S, Scholte HS, Wolfensteller U, van den Wildenberg WPM, Ridderinkhof KR (2008). Function and structure of the right inferior frontal cortex predict individual differences in response inhibition: A model-based approach. *J of Neurosci*, 28, 9790–9796.

Frank MJ, Samanta J, Moustafa AA, Sherman SJ. Hold your horses: impulsivity, deep brain stimulation, and medication in parkinsonism. *Science*. 2007;318:1309-12.

Hasbroucq T, Mouret I, Seal J, Akamatsu M. Finger pairings in two-choice reaction time tasks: Does the between-hand advantage reflect response preparation? *Journal of Motor Behavior*. 1995;27:251-262.

Hasbroucq T, Possamai CA, Bonnet M, Vidal F. Effect of the irrelevant location of the response signal on choice reaction time: An electromyographic study in humans. *Psychophysiol*. 1999;36:522-6.

Hasbroucq T, Tandonnet C, Micallef-Roll J, Blin O, Possamai CA. An electromyographic analysis of the effect of levodopa on the response time of healthy subjects. *Psychopharmacology*. 2003;165:313-6.

Hasbroucq T, Burle B, Vidal F, Possamai CA. Stimulus-hand correspondence and direct

- response activation: An electromyographic analysis. *Psychophysiol.* 2009;46:1160-9.
- Hershey T**, Revilla FJ, Wernle A, Schneider Gibson P, Dowling JL, Perlmutter JS. Stimulation of STN impairs aspects of cognitive control on PD. *Neurology.* 2004;62:1110-4.
- Herz DM**, Zavala BA, Bogacz R, Brown P. Neural Correlates of Decision Thresholds in the Human Subthalamic Nucleus. *Curr Biol.* 2016 Apr 4;26(7):916-20.
- Herz DM**, Tan H, Brittain JS, Fischer P, Cheeran B, Green AL, FitzGerald J, Aziz TZ, Ashkan K, Little S, Foltynie T, Limousin P, Zrinzo L, Bogacz R, Brown P. Distinct mechanisms mediate speed-accuracy adjustments in cortico-subthalamic networks. *Elife.* 2017 Jan 31;6. pii: e21481. doi: 10.7554/eLife.21481.
- Hübner R**, Steinhauser M, Lehle C. A dual-stage two-phase model of selective attention. *Psychol Rev.* 2010;117(3):759-84.
- Huynh H**, & Feldt LS. (1976). "Estimation of the Box correction for degrees of freedom from sample data in randomised block and split-plot designs." *Journal of Educational Statistics*, 1, 69-82.
- Hodges**, P.W., Bui, B.H. (1996). A comparison of computer-based methods for determination of onset of muscle contraction using electromyography. *Electroencephal Clin Neurophysiol*; 101: 511-9.
- Jahanshahi M**. Effects of deep brain stimulation of the subthalamic nucleus on inhibitory and executive control over prepotent responses in Parkinson's disease. *Frontiers in Systems Neuroscience.* 2013; doi: 10.3389/fnsys.2013.00118.
- Jahanshahi M**, Obeso I, Baunez C, Alegre M, Krack P. Parkinson's disease, the subthalamic nucleus, inhibition and impulsivity. *Mov Disord.* 2015;30(2):128-40.

- Limousin P, Pollak P, Benazzouz A, Hoffmann D, Le Bas JF, Broussolle E et al.** Effect of parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. *Lancet*. 1995;345:91-5.
- Martínez-Martín P, Valdeoriola F, Tolosa E, Pilleri M, Molinuevo JL, Rumià J et al.** Bilateral Subthalamic Nucleus Stimulation and Quality of Life in Advanced Parkinson's Disease. *Mov Disord*. 2002;17:372–377.
- Kumru H, Summerfield C, Valdeoriola F, Valls-Solé J.** Effects of subthalamic nucleus stimulation on characteristics of EMG activity underlying reaction time in Parkinson's disease. *Mov Disord*. 2004;19(1):94-100.
- Obeso I, Wilkinson L, Casabona E, Spekenbrink M, Luisa Bringas M, Álvarez M et al.** The subthalamic nucleus and inhibitory control: impact of subthalamotomy in Parkinson's disease. *Brain*. 2014;137:1470-80.
- Oldfield RC.** The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychol*. 1971;9: 97-113.
- Olejnik S, Algina J.** Generalized eta and omega squared statistics: measures of effect size for some common research designs. *Psychol Methods*. 2003;8(4):434-47.
- Ramdani C, Carbonnell L, Vidal F, Béranger C, Dagher A, Hasbroucq T.** Dopamine precursors depletion impairs impulse control in healthy volunteers. *Psychopharmacology*. 2015;232(2):477-87.
- Ratcliff R.** A theory of memory retrieval. *Psychol Rev*. 1978;85:59-108.
- Ratcliff R, Smith PL.** A comparison of sequential sampling models for two-choice reaction time. *Psychol Rev*. 2004;111(2):333-367.
- Ridderinkhof KR.** Activation and suppression in conflict tasks: Empirical clarification through distributional analyses. 2002. In W. Prinz & B. Hommel (Eds.), *Common*

Mechanisms in Perception and Action. *Attention & Performance XIX*, (pp 494–519).
Oxford: Oxford University Press.

Rihet P, Possamai CA, Micallef-Roll J, Blin O, Hasbroucq T. Dopamine and human information processing: a reaction-time analysis of the effect of levodopa in healthy subjects. *Psychopharmacol.* 2002;163:62-67.

Servant M, White C, Montagnini A, Burle B. Using Covert Response Activation to Test Latent Assumptions of Formal Decision-Making Models in Humans. *J Neurosci.* 2015;35:10371-85.

Servant M, White C, Montagnini A, Burle B. Linking Theoretical Decision-making Mechanisms in the Simon Task with Electrophysiological Data: A Model-based Neuroscience Study in Humans. *J Cogn Neurosci.* 2016;28(10):1501-21.

Spieser L, van den Widenberg WPM, Hasbroucq T, Ridderinkhof KR, Burle B. Controlling your impulses: electrical stimulation of the human supplementary motor complex prevents impulsive errors. *J Neurosci.* 2015;35:3010-3015.

Stauder GH. Precise onset detection of human motor responses using a whitening filter and the log-likelihood-ratio test. *IEEE Transactions on Biomed Eng.* 2001;48: 1292-305.

Sternberg S. Separate modifiability, mental modules, and the use of pure and composite measures to reveal them. *Acta Psychol (Amst).* 2001 Jan;106(1-2):147-246.

Ulrich R, Schroter H, Leuthold H, Birngruber T. Automatic and controlled stimulus processing in conflict tasks: Superimposed diffusion processes and delta functions. *Cogn Psychol.* 2015;78:148-174.

Van Boxtel GJM, Geraats LHD, Van den Berg-Lenssen MMC, Brunia CHM. Detection of EMG onset in LRP research. *Psychophysiol.* 1993;30:405–12.

Van den Wildenberg WPM, Van Boxtel GJM, Van der Molen MW, Bosch DA, Speelman JD, Brunia CHM. Stimulation of the subthalamic region facilitates the selection and

inhibition of motor responses in Parkinson's disease. *J Cog Neurosc.* 2006;18: 626-36.

Van den Wildenberg WP, Wylie SA, Forstmann BU, Burle B, Hasbroucq T, Ridderinkhof KR.

To head or to heed? Beyond the surface of selective action inhibition: a review. *Front Hum Neurosci.* 2006;4:222.

Wiecki TV, Frank MJ. A computational model of inhibitory control in frontal cortex and basal ganglia. *Psychol Rev.* 2013;120(2):329-55.

Williams D, Kuhn A, Kupsch A, Tijssen M, Van Bruggen G, Speelman H et al. The relationship between oscillatory activity and motor reaction time in the parkinsonian subthalamic nucleus. *Eur J Neurosci.* 2005;21:249-58.

Winer BJ. *Statistical Principles in Experimental Design.* 1971; New York: McGraw-Hill.

White CN, Ratcliff R, Starns JJ. Diffusion models of the flanker task: discrete versus gradual attentional selection. *Cogn Psychol.* 2011;63:210-38.

Wylie SA, Ridderinkhof KR, Elias WJ, Frysinger RC, Bashore TR, Downs KE et al. Subthalamic nucleus stimulation influences expression and suppression of impulsive behaviour in Parkinson's disease. *Brain.* 2010;133:3611-24.

Wylie SA, Claassen DO, Huizenga HM, Schewel KD, Ridderinkhof KR, Bashore TR et al. Dopamine agonists and the suppression of impulsive motor actions in Parkinson's disease. *Journal of Cognitive Neuroscience.* 2012;24:1709-1724.

Highlights

- STN stimulation's effect on impulsivity is debated.
- We propose an original approach using EMG during a conflict reaction time task
- STN DBS impaired inhibition and corrective processes, as dopaminergic treatment did.
- Only STN DBS favoured the muscular expression of fast incorrect impulses.
- Dopaminergic medication did not modify the effect of STN DBS on impulsive action control.