Dopa therapy and action impulsivity: subthreshold error activation and suppression in Parkinson's disease

Fluchère, F.; Deveaux, M.; Burle, B.; Vidal, F.; van den Wildenberg, W.P.M.; Witjas, T.; Eusebio, A.; Azulay, J.-P.; Hasbroucq, T.

DOI
10.1007/s00213-014-3805-x

Publication date
2015

Document Version
Final published version

Published in
Psychopharmacology

Psychopharmacology (2015) 232:1735–1746
DOI 10.1007/s00213-014-3805-x

ORIGINAL INVESTIGATION

Dopa therapy and action impulsivity: subthreshold error activation and suppression in Parkinson's disease

Frédérique Fluchère · Manon Deveaux · Borís Burle · Franck Vidal · Wery P. M. van den Wildenberg · Tatiana Witjas · Alexandre Eusebio · Jean-Philippe Azulay · Thierry Hasbroucq

Received: 27 May 2014 / Accepted: 6 November 2014 / Published online: 16 December 2014

Abstract
Rationale Impulsive actions entail (1) capture of the motor system by an action impulse, which is an urge to act and (2) failed suppression of that impulse in order to prevent a response error. Several studies indicate that dopaminergic treatment can induce action impulsivity in patients diagnosed with Parkinson's disease (PD). Whether this effect is due to increased impulse expression or to decreased impulse suppression remains to be deciphered.
Method We used a novel approach based on electromyographic (EMG) analyses to decipher the effects of the patient's usual dopaminergic therapy on the expression and suppression of subliminal erroneous impulses. To this end, we used a within-subject design and took advantage of the Simon task, that elicits prepotent response tendencies. The patients (N=15) performed the task on their usual dopaminergic medication and after complete medication withdrawal (for at least 12 h).
Results The correction rate that measures the ability to suppress subthreshold impulsive muscle activity was lower when the patients were on medication as compared to their off medication state ($p<0.05$). The incorrect activation rate that measures the capture of the motor system by action impulses was unaffected by medication.
Conclusions Dopa therapy affected action impulsivity. Although medication did not influence the incidence of fast action impulses, it significantly reduced patients' ability to abort and suppress muscle activation related to the incorrect response alternative.

Keywords Error control · Dopamine · Reaction time · Basal ganglia

F. Fluchère · M. Deveaux · B. Burle · F. Vidal · T. Hasbroucq
Laboratoire de Neurosciences Cognitives, Fédération de Recherche Comportement-Cerveau-Cognition, Aix-Marseille Université, CNRS, Marseille, France

F. Fluchère (✉) · T. Witjas · A. Eusebio · J.-P. Azulay
Aix-Marseille University, 13284 Marseille, France
e-mail: frederique.fluchere@ap-hm.fr

F. Fluchère · T. Witjas · A. Eusebio · J.-P. Azulay
APHM, La Timone, Department of Neurology and Movement Disorders, Pôle de Neurosciences cliniques, 13385 Marseille cedex 05, France

W. P. M. van den Wildenberg
Department of Psychology, University of Amsterdam, Amsterdam, The Netherlands

W. P. M. van den Wildenberg
Amsterdam Brain and Cognition, University of Amsterdam, Amsterdam, The Netherlands

T. Witjas · A. Eusebio · J.-P. Azulay
Institut de Neurosciences de la Timone UMR 7289, Aix Marseille University – CNRS, 13284 Marseille, France

Although dopaminergic treatment dramatically ameliorates clinical motor symptoms in Parkinson's disease (PD), its influence on cognition is more debated as both deleterious and beneficial effects have been reported (Gotham et al. 1988; Swainson et al. 2000; Cools et al. 2001, 2003; Frank et al. 2004; Bódi et al. 2009; van den Wildenberg et al. 2010; Antonelli et al. 2011; Obeso et al. 2011; Duthoo et al. 2013). The aim of the present study was to decipher the role of dopaminergic treatment on action impulsivity. Impulsive actions constitute a major source of errors and entail (1) an impulse, which is an urge to act, and (2) a lack of suppression of that impulse (DeYoung et al. 2011). Although these two components are often studied separately by resorting to distinct experimental procedures (for a review, see Dalley et al. 2008), their respective contribution to overt behavior can be estimated thanks to the Simon task (Simon and Rudell 1967). This reaction time (RT) paradigm provides an elegant

experimental context for analyzing how irrelevant information elicits incorrect action impulses that interfere with goal-directed actions (see Fig. 1). In the most common variant of this task, participants make a left- or 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 fixation point. Performance in terms of accuracy and mean RT is better when the required response corresponds spatially to the irrelevant stimulus location (congruent association) than when it does not correspond (incongruent association). This effect is termed the "Simon effect" (Simon 1990; Hommel 2011). A widely accepted interpretation of the Simon effect is that the irrelevant stimulus location automatically activates the spatially corresponding hand while the relevant stimulus color must be translated into the required response according to the task instructions (de Jong et al. 1994; Kornblum 1994; Proctor et al. 1995). If the stimulus-response association is congruent, the action impulse triggered by the irrelevant stimulus location activates the required response, thereby facilitating the correct action. In contrast, if the stimulus-response association is incongruent, the irrelevant location triggers an action impulse in the incorrect hand which must be suppressed in favor of the correct response hand. These additional operations on incongruent trials yield a cost and the performance is degraded (Kornblum et al. 1990).

This interpretation is directly supported by analyses of electromyographic (EMG) activity in healthy participants (Hasbroucq et al. 1999, 2009). Many correct response trials contain a subthreshold muscle activity in the incorrect hand, called a *partial EMG error* (Hasbroucq et al. 1999). Partial EMG errors represent fast incorrect action impulses that are successfully suppressed in order to prevent response errors. Partial EMG errors are more frequent for incongruent than for congruent trials and are associated to longer RTs than the other correct trials, thereby validating the current interpretation of the Simon effect. It must further be stressed that partial EMG errors are a unique and direct manifestation of the online detection and subsequent successful suppression of an incorrect action impulse. In contrast to response errors that result from the impulsive activation of the muscles associated with the incorrect response alternative that could not be suppressed, partial EMG errors represent the activation and successful suppression of incorrect action impulses (Burle et al. 2002). Proper assessment of action impulsivity thus requires quantifying both impulse activation and impulse suppression, two processes that can be unveiled through EMG analysis. Practically, combining response accuracy and EMG allows the specification of three trial categories that are essential to the issue of action impulsivity: (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 response (Burle and Bonnet 1999). A higher incidence of both response errors and partial EMG errors indicates increased action impulsivity (Hasbroucq et al. 2009). Of particular interest is the so-called "*correction rate*," namely the ratio between the number of partial EMG errors and the combined number of response errors and partial EMG errors. The correction rate thus represents the ability to suppress

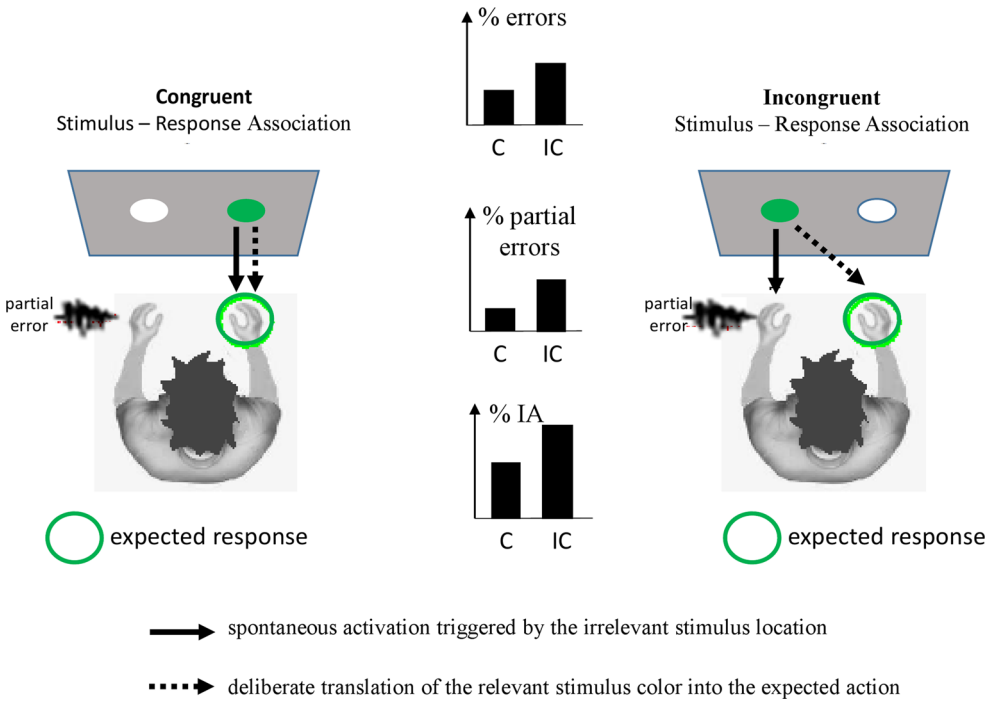

Fig. 1 Example of trials in the Simon Task. Participants were instructed to press the left button in response to a red light and a right button in response to a green light (*dashed line*). Responses are also driven by the irrelevant stimulus location, as indicated by the *solid line*. For congruent (*C*) associations, both relevant (i.e., color) and irrelevant (i.e., location) stimulus attributes activate the correct action. On incongruent (*IC*) associations, the irrelevant attribute activates an incorrect response, which interferes with the implementation of the correct response. For these IC trials, errors, partial errors, and incorrect activations (*IA*) are more important than in C trials

incorrect muscle activations in order to prevent response errors (Burle et al. 2002). Lower correction rates reflect less proficient suppression of erroneous action impulses. In the Simon task, incorrect activations (response errors and partial errors) occur on both congruent and incongruent trials, but are much more frequent on incongruent trials (Burle and Bonnet 1999; for a review, see van den Wildenberg et al. 2010). On congruent trials, incorrect activations reflect internally driven fast guesses (Yellott 1971) whereas incongruent trials contain both internally driven fast guesses and impulses triggered by the external irrelevant stimulus location. Since fast guesses do not depend on congruency, differences in the frequency of incorrect activations between incongruent and congruent trials reflect the expression of impulses triggered by the irrelevant stimulus location (Hasbroucq et al. 1999).

Here, we quantify the effect of dopaminergic treatments on covert impulse control, i.e., on the activation and suppression of impulsively triggered muscle activity. We predicted that if patients are more susceptible to reacting impulsively to external stimuli when taking dopaminergic medication, then the combined number of fast partial EMG errors and response errors, especially on incongruent trials, should be larger compared to their off medication state. While if dopa therapy impairs the proficiency to suppress prepotent but incorrect action impulses, then the correction rate for both congruent and incongruent trials should be lower.

Materials and methods

Participants

Sixteen inpatients (four women) with idiopathic PD participated in this study. All gave written informed consent according to the convention of Helsinki, and the study was approved by the local research ethics committee (Comité de Protection des Personnes Sud Méditerranée I). They were recruited from the Department of Neurology and Movement Disorders, University Hospital La Timone (Marseille, France). All these patients were hospitalized in order to perform presurgery evaluations and were at the same stage of the disease. One patient could not complete the task and was discarded from the study.

All patients received oral dopaminergic treatment (levodopa and dopamine agonists). Table 1 and 2 present the clinical data of the 15 retained patients. All patients were right-handed, according to the Edinburgh Handedness inventory (Oldfield 1971). They were aged between 41 and 69 years (M=60 years, SD=7 years). The mean disease duration was 12 years (SD=6 years) and the mean Hoehn and Yahr score was 3 in the off medication state. Neuropsychological (Mini-Mental State Examination—MMSE—and Mattis scale) and mood (Beck Depression Inventory—BDI) tests were performed to exclude patients with cognitive deterioration or major depressive syndrome. The cutoff of 24 out of 30, 130 out of 144, and 20 out of 60 were used respectively for the MMSE, the Mattis scale, and for the BDI. The various cutoff scores are based on standard clinical limits to define cognitive impairment or depressive syndrome. 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 included history of other neurological disorders, dyschromatopsia, uncorrected visual impairment, severe and disabling dyskinesia, or tremor (with a score ≥3 out of 4 in the Unified Parkinson's Disease Rating Scale (UPDRS) part III) (Table 2).

Table 1 Demographic characteristics, levodopa equivalent daily dose

Patient	Gender	Age (years)	PD duration (years)	LEDD (mg)
1	F	69	14	1,300
2	M	63	9	1,225
3	M	62	28	910
4	M	64	8	975
5	M	66	17	1,500
6	F	60	11	1,050
7	F	41	6	1,100
8	M	65	10	1,600
9	M	57	7	1,500
10	M	56	8	1,450
11	M	67	8	1,325
12	F	61	20	1,750
13	M	59	7	1,400
14	M	64	8	1,495
15	M	51	12	1,325
Mean	–	60	12	1,327
SD	–	7	6	239

Fifteen patients (four women) with idiopathic Parkinson's disease were tested in this study. They were aged between 41 and 69 years (M=60 years, SD=7 years), the mean disease duration was 12 years (SD=6 years). All patients were right-handed. The medication dosage was set to achieve the best therapeutic effect for each patient. The patients were tested in two conditions: off medication and on medication. The on medication condition corresponded to the patient's usual medication (L-dopa+dopaminergic agonists except for patient 8 whose medication was only L-dopa) and the experimental session performing during the "best on" of each patient. The off medication condition was run after an overnight withdrawal of all dopaminergic treatment (at least 12 h)

LEDD levodopa equivalent daily dose, *M* male, *F* female

Apparatus and stimuli

The experiment took place in a dimly lit room. Comfortably seated on an armchair, the subject faced a black plastic board on which the stimuli were presented. The distance between

Table 2 Clinical data of the patients

Patient	Hoehn and Yahr	UPDRS III (/108)		MMSE (/30)	Mattis (/144)	BDI (/63)
	Med Off (/5)	Med Off	Med On			
1	2.5	16	7	30	132	7
2	2	14	2	28	140	8
3	2	16	8	28	138	4
4	3	29	13	29	136	14
5	3	26	6	29	135	9
6	3	16	2	29	141	5
7	3	25	12	30	138	9
8	3	32	20	29	144	10
9	2	14	3	30	144	20
10	2	19	6	30	141	20
11	2	21	7	29	136	2
12	2.5	18	0	27	137	7
13	3	20	7	26	125	11
14	2.5	26	11	29	136	5
15	2	27	5	29	144	12
Mean	3	21*	7*	29	138	10
Range	0	14–32	0–20	26–30	132–144	2–20

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 Med Off UPDRS III and Med On UPDRS III : <0.0001

this display and the subject's eyes was 1.80 m. A blue light-emitting diode (LED) fixed on the center of the display served as a fixation point. The stimuli were delivered by two bicolor (red/green) LEDs located on the left and right of the fixation point, the distance between these LEDs subtended 3.2° of visual angle. A pull-out plastic table (100×50 cm) was disposed in front of the subject. Two plastic cylinders (3 cm in diameter, 10 cm in height) were fixed 32 cm apart on the table and 16 cm on the left and right of the subject's midsagittal plane and served as handgrips. A force sensor (Model 1042, Tedea-Huntleigh, Cardiff UK) was fixed on the top of each cylinder. The subject 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 and was to be performed within 1.5 s following the stimulus. When one of the lateral LEDs was lit, the association was either congruent or incongruent, depending on whether the correct response was on the same side or on the opposite side as the signal.

Procedure and design

Throughout the test, an experimenter sat next to the participant. Another experimenter managed the computer programs in an adjacent room. Each trial started with the blue fixation point coming on. One second later, one of the two lateral bicolor diodes displaying the stimuli was illuminated either in green or in red. The color and location of the stimuli were unpredictable. The subject had to press the right or the left force sensor depending on the color of the stimulus. He (she) was told to respond 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 the stimulus, the trial ended the same way. The next trial started 1.5 s later. The trials were presented in blocks of 64, in which each type of stimulus was equiprobable. Each experimental session comprised 6 blocks of 64 trials and lasted 20–25 min. Between blocks, the subject was provided a few minutes rest. The subjects were trained during an initial training session (one block of 64 trials) and were thereafter tested on two experimental sessions on 2 separate days. Each session corresponded to the medication status (Off or On). The "off medication" condition was run after an overnight withdrawal of all dopaminergic treatment (for at least 12 h) whereas the "on medication" condition corresponded to the patient's regular medication (L-dopa and dopaminergic agonists). The experimental session was performed during the "best on" state for each patient. The best on condition is classically defined by the moment where the usual dopaminergic treatment is the most effective, that is between 1 and 2 h after L-dopa intake. Before each experimental session, motor condition was assessed by the UPDRS, part III. Color-response mapping instructions were counterbalanced across participants, as well as session order (on vs. off). Eight patients had to press the left force sensor when the stimulus was green, and the right force sensor when the stimulus was red. The other eight patients received the reverse mapping instructions. In each of these two groups, half of patients started with the off medication condition, the other half started on medication. Counterbalancing session order overcomes retest effects.

Signal recordings and processing

The EMG activity of the flexor pollicis brevis was recorded bipolarly by means of surface Ag-AgCl electrodes (BIOSEMI Active-Two electrodes, Amsterdam), 6 mm in diameter, fixed about 10 mm apart on the skin of the thenar eminence. The EMG activity was amplified, and the sampling rate was 1,024 Hz (Filters: DC to 268 Hz, 3 dB/octave). The EMG signal was continuously monitored by the experimenter in order to avoid as much as possible any background activity in order to facilitate the EMG onset detection. If the signal became noisy, the experimenter immediately asked the subject to relax his (her) muscles.

It was important for the present purpose to detect the smallest incorrect muscular activations. To this end, 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), the ultimate standard, against which the accuracy of the different algorithms is rated, remains visual inspection (see Staude 2001). To overcome subjective influence on the scoring, the experimenter who processed the signals was unaware of the type of associations (congruent, incongruent) or medication status (on, off) to which the traces corresponded.

Data analysis

The data recorded during the training session were not analyzed. To be classified as a partial error trial, the EMG signal deflection had to be phasic and return to baseline (rest) level before the onset of the EMG activity related to the button-press response (see Fig. 2a). Partial errors were not confused with tremor as Parkinsonian tremor is typically a 5-Hz rhythmic movement (see Fig. 2b). Response errors and partial errors were detected and counted. The correction rate (CR) was defined as:

$$CR = Npe/(Npe + Ner)$$

where Npe reflects the number of partial error trials and Ner the number of response error trials. In other words, the CR reflects the number of successfully corrected incorrect activations divided by the overall number of incorrect activations (irrespective of correction). The correction rate is thus the proportion of incorrect muscle activations that were successfully suppressed and therefore did not turn into response errors.

The chronometric variables analyzed in the present study are illustrated in Fig. 2. RT was defined as the latency between stimulus onset and the EMG onset of the correct response. We also measured correction time, or the interval between the onset of the partial error and the EMG onset of the correct response.

The dynamics of action impulsivity are revealed by the "conditional incorrect activation function" (CIAF). Such functions are analogous to traditional conditional accuracy functions (for an overview, see Ridderinkhof 2002) but plot incorrect activation rates (rather than behavioral response accuracy rates) against latency. Latency distributions for all trials (overt response errors, partial errors, and correct responses) were first Vincentized (Vincent 1912; Jianq et al. 2004). Vincentizing (quantile averaging) is an efficient means of pooling RT distributions across individuals to produce a group average. The procedure, which was popularized by Ratcliff (1979), is named after biologist S. B. Vincent (1912), who developed it for constructing learning curves at the beginning of the last century. The benefit of Vincentizing is that the resulting histogram is the average of the individuals' distributions (i.e., the mean of the Vincentized distribution is the mean of the individuals' means and the standard deviation of the Vincentized distribution is the mean of the individuals' standard deviations), so that each individual contributes equally to each bin of the Vincentized distribution (while the rough distribution would be biased by individual differences: the fastest participants would contribute more to the left part and the slowest participants would contribute more to the right part). For congruent and incongruent associations separately, RTs were rank-ordered and partitioned into five bins (quintiles; bins 1–5), each bin containing 20 % of the trials. Incorrect activation rates (number of response errors and partial errors/number of trials) were then calculated for each bin, thus generating five incorrect activation values each for congruent and incongruent association types of trials. These incorrect activation rates were then plotted against the average RT for each bin.

Stronger action impulsivity is associated with a higher percentage of incorrect activations. The dynamics of impulse expression for each level of congruency was thus inferred from the pattern of incorrect activations for the five bins.

The analyses of variance (ANOVAs) reported in the next section involved congruency of the stimulus-response association (congruent, incongruent) and medication (on, off) as within-subject variables. For distribution analyses, bin (1–5) was added as a third factor in the ANOVA. Proportions (errors, partial errors, incorrect activations, correction rate) were arcsine transformed to stabilize their variance before being submitted to an ANOVA (see Winer 1971, p. 221).

Results

Discarded trials

Due to tonic activity, tremor, omissions, or artifacts preceding the contraction involved in the response, 1.72 % of the trials were rejected (see Fig. 2).

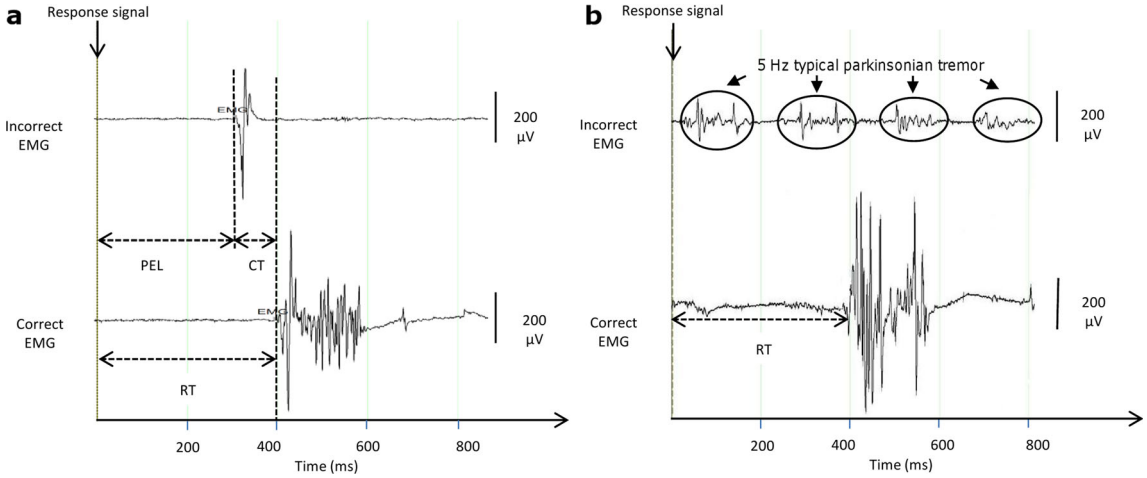

Fig. 2 Electromyographic activity in the involved (*correct EMG activation*) and noninvolved (*incorrect EMG activation*) agonists. **a** Traces recorded during a partial EMG error trial showing the electromyographic activity (in mV) of the agonists of the two responses as a function of time (in ms) from the onset of the response signal (time 0). *Lower trace*: correct activity. *Upper trace*: incorrect activity. *RT* reaction time (from signal to EMG onset of the correct response); *PEL* partial error latency (from signal to EMG onset of the transient partial EMG error); *CT* correction time (from the onset of the partial EMG error to the EMG onset of the correct response). In contrast to tremor which causes tonic rhythmic pulses (**b**), partial EMG errors consist in 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 seldom (1.72 %), which is compatible with clinical observations showing that tremor and dystonia disappear when PD patients engage a task

Response errors

Response errors occurred on 2.87 % of the trials. Patients made more response errors for incongruent (4.26 %) than for congruent associations (1.48 %), $F(1,14)=16.36$, $p<0.01$, and when they were on (3.42 %) compared to when they were off medication (2.32 %), $F(1,14)=6.15$, $p<0.05$. The interaction between medication and congruency was not significant, $F(1,14)<1$. These results are illustrated in Fig. 3a.

Partial errors

Partial EMG errors occurred on 29.65 % of the correct trials. They were more frequent for incongruent (38.25 %) than for congruent (21.09 %) associations, $F(1,14)=53.63$, $p<0.01$. There was a nonsignificant tendency for patients to make more partial EMG errors when they were on medication (31.33 %) compared to off medication (27.97 %), $F(1,14)=4.01$, $p=0.06$. There was no interaction between medication and congruency, $F(1,14)=2.87$, $p=0.12$.

Incorrect activations (combining response errors and partial errors)

Incorrect activation trials (overt response errors and partial errors combined) were more frequent for incongruent (42.47 %) than for congruent associations (22.25 %), $F(1,14)=61.84$, $p<0.01$. There was no influence of medication, neither as a main effect, $F<1$, nor as a component term in interaction with congruency, $F(1,14)=1.71$, $p=0.21$. These results are illustrated in Fig. 3a.

CIAF analyses revealed an interaction between congruency and bin: The difference in incorrect activation rate between incongruent and congruent associations was more pronounced at relatively short latencies and progressively vanished as the latency of incorrect activation increased, $F(4,56)=9.72$, $p<0.01$. No interaction between bin and any other factor reached significance (all Fs<1). This pattern of results, illustrated in Fig. 4, suggests that medication exerted no effect on action impulsivity defined as short-latency muscle activity in the incorrect hand.

Correction rate

The correction rate was lower for incongruent (90.35 %) than for congruent (94.5 %) associations, $F(1,14)=8.96$, $p<0.01$. It was significantly reduced when the patients were on medication (90 %) as compared to their off medication state (94.85 %), $F(1,14)=5.66$, $p<0.05$. There was no hint of an interaction between medication and congruency ($F<1$). Medication thus impaired the ability to correct action impulses defined as the ability to suppress muscle activity in the incorrect hand. These results are illustrated in Fig. 3b.

Response latency

Pure correct trials The results are presented in Fig. 5. RT was shorter for congruent (311 ms) than for incongruent (354 ms) associations, $F(1,14)=15.09$, $p<0.01$. Neither medication nor

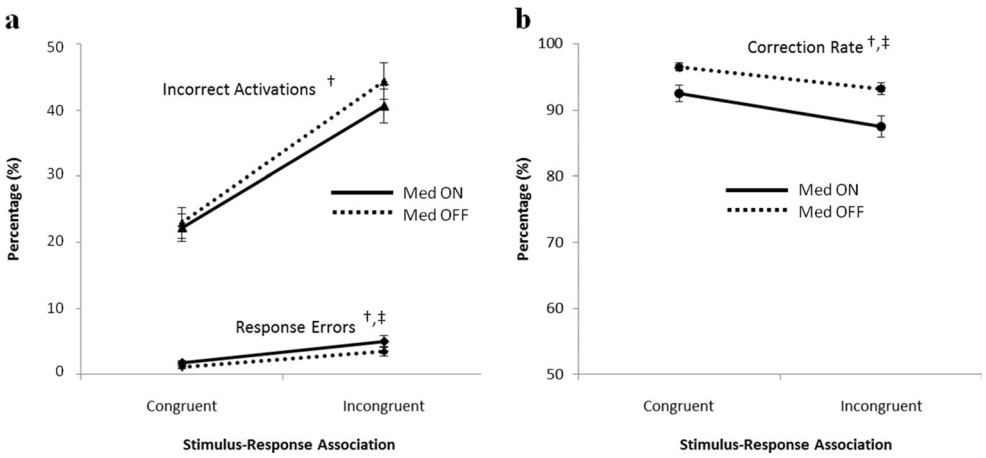

Fig. 3 Percentages (ordinate) of response errors, incorrect activations (**a**) and correction rate (**b**) as a function of congruency (abscissa), and medication status (parameter, *full lines*: On medication, *dotted lines*: Off medication). *Error bars* indicate SEs. *Dagger* = congruent versus Incongruent trials with $p<0.05$. *Double dagger* = on medication versus off medication with $p<0.05$

the interaction between congruency and medication were significant (both Fs<1).

Partial error trials The results are presented in Fig. 5. Partial error latency was affected neither by congruency nor by medication (both Fs<1). The interaction between these factors was also far from significant ($F<1$). Correction time was shorter for congruent (242 ms) than for incongruent (255 ms) associations, $F(1,14)=4.69$, $p<0.05$. Correction time was further shorter when patients were on medication (230 ms) as compared to the off state (267 ms), $F(1, 14)=5.33$, $p<0.05$. There was no interaction between medication and congruence ($F<1$).

Relation between medication dosage, incorrect activations, and correction rate

We computed Spearman's rank correlation coefficients between medication dosage and the number of incorrect activations and the correction rate when the patients were on medication. There was no hint of a relation between medication dosage and the number of incorrect activations ($\rho=0.17$, $p=0.532$). There was no significant relation between medication

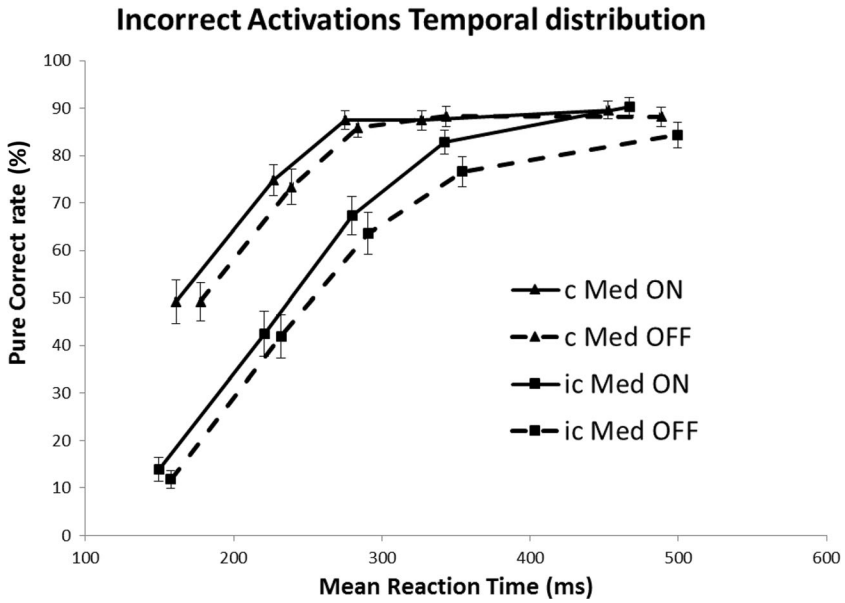

Fig. 4 Incorrect activation temporal distribution. Conditional incorrect activations functions for congruent (*triangles*) and incongruent associations (*squares*) when the patients where on medication (*solid lines*) and off medication (*dotted lines*). *Error bars* indicate SEs. Incorrect activations on incongruent trials were associated with short latencies. Throughout the entire distribution, medication exerted no significant effect. Note that in the first bin, for incongruent trials, the frequency of incorrect activations is about 87 %, that is clearly above chance level. Such a high percentage of incorrect response activation discards the possibility that partial errors simply reflect guesses/premature responding, since guesses should yield accuracy rates around chance level. In the same bin, the frequency of incorrect activations is 51 % which indicates that the patients responded at chance level. Note further that the difference in the frequency of incorrect activations between congruent trials and incongruent trials estimates the proportion of trials triggered by the irrelevant stimulus location (e.g., 36 % in the first bin)

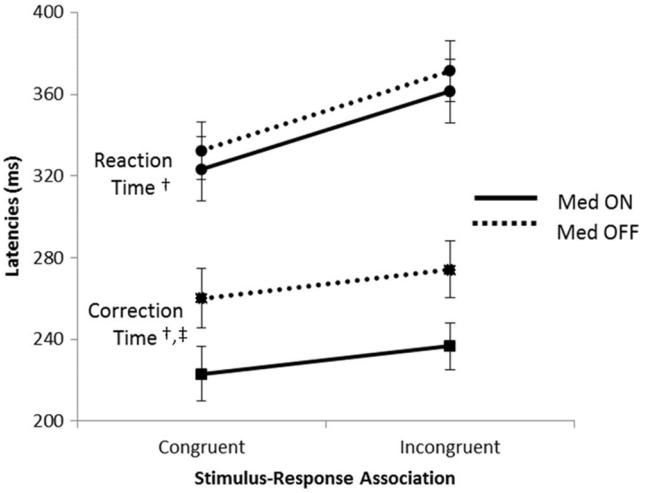

Fig. 5 Mean latency (in ms) of EMG onset associated with pure correct trials (*upper*) and mean correction time (in ms) for partial error trials as a function of medication status. (*solid lines*: on medication; *dotted lines*: off medication) for congruent and incongruent trials. *Error bars* indicate SEs. *Dagger*=congruent versus Incongruent trials with $p<0.05$. *Double dagger*=on medication versus off medication with $p<0.05$

dosage and the correction rate ($\rho=0.401$, $p=0.138$). We also tested whether the effect of medication on the correction rate depended on baseline correction rate but could find no evidence for such a relationship ($\rho=0.01$, $p=0.95$).

Discussion

The aim of the present study was to determine the effects of regular dopaminergic medication on action impulsivity in PD patients by specifically taking into account impulsive activation of muscles related to incorrect responses. During regular dopaminergic medication (levodopa and dopamine agonists) and 12 h after medication withdrawal, PD patients performed the Simon task that induces erroneous response tendencies that should be overridden. By analyzing EMG activity, we could assess the influence of this pharmacological treatment on the activation and suppression of impulsive action tendencies; information that is lost if analyses are confined to overt responses. Before evaluating the implications of the role of dopamine and basal ganglia in action control, the main findings are discussed first.

Behavioral effects and trial classification

Performance in terms of overall accuracy and RT was better for congruent than for incongruent stimulus-response associations which indicates that in PD patients, like in healthy subjects, the task-irrelevant spatial correspondence between the stimulus location and the correct response hand interferes with voluntary action control (Praamstra et al. 1998; Praamstra and Plat 2001; Schmiedt-Fehr et al. 2007; Wylie et al. 2010). Patients committed more response errors when they were on their regular dopaminergic medication as compared to their off state (for a discussion on the effect of levodopa on healthy subjects' performance, see Rihet et al. 2002). The increase in response error rate was not accompanied by changes in RT, excluding an interpretation of the effect of medication on accuracy in terms of speed-accuracy trade off (Pachella 1974; Rinkenauer et al. 2004). Note that Wylie et al. (2010) reported no significant effects of dopamine agonists on response accuracy in the Simon task but the effect was numerically in the same direction as in the present study. We shall comment the difference between the present results and their findings in what follows.

Although our patients did not exhibit severe and disabling dyskinesia or tremor, one might think that their motor symptoms could preclude the distinction of partial EMG errors trials from pure correct and response error trials. Partial EMG errors cannot be confounded with tremor because they consist in single phasic bursts rather than in tonic rhythmic pulses (see Fig. 2). It must also be noted that partial EMG errors were not equally distributed across experimental conditions but occurred more frequently on incongruent than on congruent trials, as in previous studies in healthy subjects (Hasbroucq et al. 1999, 2009; Burle et al. 2002). In our patients like in healthy subjects, partial EMG errors thus reflect impulse activation rather than intercurrent muscle twitches (e.g., due to tremor or dystonia) which occurrence would be task-unrelated. Furthermore, as observed in healthy subjects (Smid et al. 1990), (1) RTs of partial error trials were longer than RTs of pure correct trials and (2) congruency affected the patients' correction time. The correction that follows a partial EMG error thus involves reprocessing part of the information conveyed by the visual stimulus. This argues in favor of the notion that partial EMG errors reflect erroneous action impulses that are suppressed and corrected. The replication, in the present study, of those findings indicates that partial EMG error trials were correctly classified in our patients. Note that previous work in healthy subjects has shown that on trials following a partial EMG error trial, RT is lengthened (Allain et al. 2009), just like after making a response error (Rabbit 1966), although the slowing down is less pronounced. Partial errors have an electroencephalographic correlate, the Ne (Falkenstein et al. 1991) or ERN (Gehring et al. 1993) that is comparable to that of response errors (Scheffers et al. 1996; Vidal et al. 2000; Roger et al. 2010; Bonini et al. 2014). These findings demonstrate that incorrect muscle activity drives both partial EMG errors and response errors, but the incorrect impulse is successfully suppressed on partial error trials only. Analyses of partial EMG errors thus extend the reduced accuracy rates observed under medication at the behavior level.

Dopaminergic medication and the expression of action impulsivity

Incorrect muscle activations were more frequent on incongruent than on congruent trials, reflecting that the irrelevant stimulus location captures the motor system. The CIAF distribution analysis showed that this capture was not homogeneously distributed over time. Congruency essentially affected the fastest incorrect muscle activations and its influence vanished with increasing activation latency. These dynamics are in line with current interpretations of the Simon effect on response errors in healthy subjects (Kornblum et al. 1990; Ridderinkhof 2002). These hold that early during the RT interval on incongruent trials, the irrelevant stimulus location activates the urge to make a fast incorrect response. Here, we show that on a large proportion of incongruent trials, this stimulus-driven urge is best expressed in quantifiable short-latency muscle contractions (Hasbroucq et al. 1999). With time, the activation of the correct response replaces this initial incorrect urge, which is reflected by a diminution of the frequency of incorrect activations for incongruent trials for longer RTs. Importantly, medication did not influence the incidence of incorrect muscle activity. Although null results should be interpreted with caution, this pattern suggests that medication does not affect the incidence of action impulsivity triggered by irrelevant stimulus dimensions.

In their study on dopamine agonists and response errors, Wylie et al. (2012) reported that medication had no effect on overall accuracy rates but tended to increase the Simon effect on mean behavioral accuracy. Distributional analyses confirmed that patients made fast response errors on incongruent trials, a pattern that was not influenced by administration of agonists. From this, they concluded that, compared with an off-agonist state, patients on their on agonists state were no more susceptible to reacting impulsively. It should be remarked that this conclusion was based on response errors. However, the number of response errors is a poor reflection of the number of incorrect muscle contractions. Note that in the current study, response errors were about ten times less frequent than the total number of trials with incorrect muscle activity. In addition, classifying trials on the basis of response accuracy does not distinguish between pure correct trials and trials with partial EMG errors. The response error rates observed by Wylie and colleagues therefore might not be sensitive to medication-induced variations in the subthreshold activation and suppression of impulsive muscle activity. Despite this limitation, the conclusions of Wylie et al. are partly in line with the present study: Dopa therapy seems to exert virtually no effect on the rate of short-latency incorrect activations, computed from the sum of response errors and partial EMG errors.

Dopaminergic medication and the suppression of action impulsivity

Although dopa therapy ameliorates clinical motor symptoms in PD, cognitive processing may be affected as well (Cools et al. 2001; Frank et al. 2004; Bódi et al. 2009). The present study shows that under pharmacological treatment, patients are less proficient in suppressing subthreshold muscular activation. At first sight, this conclusion might seem at odds with the results of Obeso et al. (2011). These authors reported no effect of levodopa withdrawal on stop task performance. The stop task measures the ability to suppress ongoing processing upon an explicit stop signal (Logan and Cowan 1984). There is evidence that such a suppression exerts global rather than selective effects on the motor system. For instance, when inhibition of a thumb response is required, the stop signal caused not only a reduction in the excitability of the cortical zones controlling the thumb response but also a reduction in the excitability of the cortical area controlling task-irrelevant leg muscles (Badry et al. 2009). While the stop task allows inferences about global suppression in isolation, the Simon task provides the context for assessing the effect of medication on impulse expression and selective suppression. Indeed, in this task, the suppression of a specific response relies on a conditional rule: "suppress the activated erroneous response but not the required correct response." Importantly, the distinction between global and selective suppression is anatomo-functionally grounded. Aron and colleagues (Aron and Poldrack 2006; Jahfari et al. 2010) have stressed the role of the subthalamic nucleus (STN) in the global suppression of action. Using the stop task, these authors showed by functional magnetic resonance imaging in healthy participants that the STN was activated in the suppression of actions initiated voluntarily but later signaled to be inappropriate (Aron and Poldrack 2006). These studies point to the hyperdirect pathway linking the frontal cortex to the STN for implementing global suppression. Aron (2011) recently suggested that in contrast to global suppression, selective suppression relies on the indirect striatum-globus pallidus externus (GPe)–STN pathway of the basal ganglia. While as a structure, the STN is involved in both pathways, it is possible that the hyperdirect and indirect pathways impinge onto different populations of STN neurons (Aron 2011). The population recruited via the hyperdirect pathway would be involved in global suppression while the population recruited via the indirect pathway would be involved in selective suppression. In light of the results obtained by Obeso et al. (2011) with the stop task, the effects obtained in the present study suggest that dopa therapy impairs selective suppression by acting on the indirect dopaminergic pathway while being ineffective on global suppression mediated by the glutamatergic hyperdirect pathway. Recent work suggests that global suppression can be affected by noradrenergic medication (Kehagia et al. 2014).

Dopaminergic medication and the replacement of incorrect impulses

An additional merit of the present EMG approach is that it reveals online control processes to replace a partial EMG error by the correct response. The correction time reflects the latency of the processes that replaces an activation of the incorrect muscle by the activation of correct response-related muscles. In contrast with partial error latency, which was unaffected by medication, the correction time was significantly shorter when the subjects were on medication than after medication withdrawal, revealing that dopa therapy may selectively speed up partial error replacement. Since neither RT of pure correct trials nor the latency of partial errors were affected by medication, this chronometric effect is specific to error replacement processes and can hardly be interpreted in terms of motor threshold variation. In conjunction with the effects on the correction rate, it suggests that on medication as compared to off medication, patients were less efficient in replacing erroneous action impulses, but if suppression succeeded then partial errors were replaced faster. This drug-induced specific speed-accuracy tradeoff deserves to be studied further. To this end, future research should test larger patient samples and address the respective effects of dopamine agonists and levodopa. The involvement of cerebral structures in this tradeoff could be investigated thanks to electroencephalographic techniques according to the neurobiological model sketched below.

Sketching a model of dopamine influences on partial error suppression and replacement

Electroencephalographic (Burle et al. 2008) results indicate that both correct responses and incorrect response activations (partial errors) are generated by the primary motor cortex. There is general agreement that the frontal lobes make a critical contribution to the suppression of incorrect response activations (see Hampshire et al. 2011; Munakata et al. 2011). Functional magnetic resonance data recorded during the performance of the stop task suggest that reactive suppression is implemented thanks to the co-activation of a functional network comprising multiple functionally distinct subregions of the right inferior frontal sulcus and of the supplementary motor area (Erika-Florence et al. 2014) rather than a unique inhibitory module. A recent local field potential study (Bonini et al. 2014) illustrates the role of the SMA proper (SMAp), a fronto-central cortical area which activity is dopamine dependent (for a review, see Holroyd and Coles 2002). The SMAp receives extensive projections from the basal ganglia (Akkal et al. 2007) where, in medicated PD patients, levodopa and dopamine agonists converge in restoring dopamine concentrations. This treatment affects both D1 and D2 receptors which contribute differently to the direct and indirect striatal pathways. D1 receptors are more involved in the direct pathway that releases actions while D2 receptors contribute more to the indirect pathway which is involved in suppressing actions (Claffey et al. 2010; Aron and Verbruggen 2008; Aron 2007). When binding to D1 receptors, dopamine activates the direct pathway whereas it inhibits the indirect pathway when binding to D2 receptors. Levodopa has affinity to both D1 and D2 receptor types. In contrast, dopamine agonists have higher affinity for D2-like receptors. In all but one patients of the present study, medication comprised both levodopa and dopamine agonists. We suggest that this drug association biased the balance toward D2 receptors. Because the activation of D2 receptors putatively inhibits the indirect pathway via the subthalamic nucleus, medication should reduce basal ganglia output to the SMAp. This, in turn, would reduce the activity of the SMA and impair partial error control.

Limitations of the present study

Although the limited sample size did allow us to show that medication impairs the correction rate of impulse action tendencies at the group level, it may have precluded detailed correlational analyses of medication dosage and the patient's individual ability to correct erroneous impulses. Future studies might address this issue with larger sample sizes and might take into account baseline levels of performance, as it is known that dopamine-related changes on performance measures of cognitive control depend on baseline performance when patients are withdrawn (e.g., Wylie et al. 2012). Another issue is related to our within-subject design that limits the interpretation of the findings to PD patients hospitalized in order to perform presurgery evaluations. One advantage of such a sample is to be relatively homogenous: the patients were at the same stage of the disease. It must be acknowledged that the patient population is peculiar because such patients have suffered from PD for a long period. For these patients, however, the comparison can be considered as powerful and informative. In order to assess the effect of medication per se on impulse activation and suppression, future studies should contrast the performance of PD patients to that of healthy age-matched controls on and off medication.

Conclusion

To sum up, in addition to ameliorating clinical motor symptoms, dopa therapy clearly increased action impulsivity. Although medication did not influence the incidence of fast action impulses, it significantly reduced patients' ability to suppress muscle activation related to the incorrect response alternative.

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

References

Akkal D, Dum RP, Strick PL (2007) Supplementary motor area and presupplementary motor area: targets of basal ganglia and cerebellar output. J Neurosci 27:10659–10673

Allain S, Burle B, Hasbroucq T, Vidal F (2009) Sequential adjustments before and after partial errors. Psychon Bull Rev 16:356–362

Antonelli F, Ray N, Strafella AP (2011) Impulsivity and Parkinson's disease: more than just disinhibition. J Neurol Sci 310:202–207

Aron AR (2007) The neural basis of inhibition in cognitive control. Neuroscientist 13:214–228

Aron AR (2011) From reactive to proactive and selective control: developing a richer model for stopping inappropriate responses. Biol Psychiatry 69:E55–E68

Aron AR, Poldrack RA (2006) Cortical and subcortical contributions to Stop signal response inhibition: role of the subthalamic nucleus. J Neurosci 26:2424–2433

Aron AR, Verbruggen F (2008) Stop the presses: dissociating a selective from a global mechanism for stopping. Psychol Sci 19:1146–1153

Badry R, Mima T, Aso T, Nakatsuka M, Abe M, Fathi D et al (2009) Suppression of human cortico-motoneuronal excitability during the stop-signal task. Clin Neurophysiol 120:1717–1723

Bódi N, Kéri S, Nagy H, Moustafa A, Myers CE, Daw N, Dibó G, Takáts A, Bereczki D, Gluck MA (2009) Reward-learning and the novelty-seeking personality: a between- and within-subjects study of the effects of dopamine agonists on young Parkinson's patients. Brain 132:2385–2395

Bonini F, Burle B, Liégeois-Chauvel C, Régis J, Chauvel P, Vidal F (2014) Action monitoring and medial prefrontal cortex: leading role of supplementary motor area. Science 343:888–891

Burle B, Bonnet M (1999) What's an internal clock for? From temporal information processing to temporal processing of information. Behav Process 45:59–72

Burle B, Possamai CA, Vidal F, Bonnet M, Hasbroucq T (2002) Executive control in the Simon effect: an electromyographic and distributional analysis. Psychol Res 66:324–336

Burle B, Roger C, Allain S, Vidal F, Hasbroucq T (2008) Error negativity does not reflect conflict: a re-appraisal of conflict monitoring and anterior cingulate cortex activity. J Cogn Neurosci 20:1637–1655

Christenson GA, Faber RJ, de Zwaan M (1994) Compulsive buying: descriptive characteristics and psychiatric comorbidity. J Clin Psychiatry 55:5–11

Claffey MP, Sheldon S, Stinear CM, Verbruggen F, Aron AR (2010) Having a goal to stop action is associated with advance control of specific motor representations. Neuropsychologia 48:541–548

Cools R, Barker RA, Sahakian BJ, Robbins TW (2001) Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. Cereb Cortex 11:1136–1143

Cools R, Barker RA, Sahakian BJ, Robbins TW (2003) L-Dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease. Neuropsychol 41:1431–1441

Dalley JW, Mar AC, Economidou D, Robbins TW (2008) Neurobehavioral mechanisms of impulsivity: fronto-striatal systems and functional neurochemistry. Pharmacol Biochem Behav 90(2):250–260

de Jong R, Liang CC, Lauber E (1994) Conditional and unconditional automaticity: a dual-process model of effects of spatial stimulus–response correspondence. J Exp Psychol Hum Percept Perform 20:731–750

DeYoung CG, Cicchetti D, Rogosch FA, Gray JR, Eastman M, Grigorenko EL (2011) Sources of cognitive exploration: genetic variation in the prefrontal dopamine system predicts openness/intellect. J Res Pers 45(4):364–371

Duthoo W, Braem S, Houtman F, Schouppe N, Santens P, Notebaert W (2013) Dopaminergic medication counteracts conflict adaptation in patients with Parkinson's disease. Neuropsychol 27:556–561

Erika-Florence M, Leech R, Hampshire A (2014) A functional network perspective on response inhibition and attentional control. Nat Commun 5:4073

Falkenstein M, Hohnsbein J, Hoormann J (1991) Effects of crossmodal divided attention on late ERP components: II. Error processing in choice reaction time tasks. Electroencephalogr Clin Neurophysiol 78:447–455

Frank MJ, Seeberger LC, O'reilly RC (2004) By carrot or by stick: cognitive reinforcement learning in Parkinsonism. Science 306:1940–1943

Gehring WJ, Goss B, Coles MGH, Meyer DE, Donchin E (1993) A neural system for error detection and compensation. Psychol Sci 4:385–390

Gotham AM, Brown RG, Marsden CD (1988) Frontal cognitive function in patients with Parkinson's disease on and off levodopa. Brain 111:299–321

Hampshire A, Thompson R, Duncan J, Owen AM (2011) Lateral prefrontal cortex subregions make dissociable contributions during fluid reasoning. Cereb Cortex 21(1):1–10

Hasbroucq T, Possamaï CA, Bonnet M, Vidal F (1999) Effect of the irrelevant location of the response signal on choice reaction time: an electromyographic study in humans. Psychophysiology 36:522–526

Hasbroucq T, Burle B, Vidal F, Possamaï CA (2009) Stimulus-hand correspondence and direct response activation: an electromyographic analysis. Psychophysiology 46:1160–1169

Hodges PW, Bui BH (1996) A comparison of computer-based methods for determination of onset of muscle contraction using electromyography. Electroencephal Clin Neurophysiol 101:511–519

Holroyd CB, Coles MG (2002) The neural basis of human error processing: reinforcement learning, dopamine, and the error-related negativity. Psychol Rev 109:679–709

Hommel B (2011) The Simon effect as tool and heuristic. Acta Psychol 136:189–202

Jahfari S, Stinear CM, Claffey M, Verbruggen F, Aron AR (2010) Responding with restraint: what are the neurocognitive mechanisms? J Cogn Neurosci 22:1479–1492

Jianq Y, Rouder JN, Speckman PL (2004) A note on the sampling properties of the Vincentizing (quantile averaging) procedure. J Math Psychol 48:186–195

Kehagia AA, Housden CR, Regenthal R, Barker RA, Müller U, Rowe J, Sahakian BJ, Robbins TW (2014) Targeting impulsivity in Parkinson's disease using atomoxetine. Brain. doi:10.1093/brain/awu117

Kornblum S (1994) The way irrelevant dimensions are processed depends on what they overlap with: the case of Stroop- and Simon-like stimuli. Psychol Res 56:130–135

Kornblum S, Hasbroucq T, Osman A (1990) Dimensional overlap: cognitive basis for stimulus–response compatibility—a model and taxonomy. Psychol Rev 97:253–270

Logan GD, Cowan WB (1984) On the ability to inhibit thought and action: a theory of an act of control. Psychol Rev 91:295–327

Munakata Y, Herd SA, Chatham CH, Depue BE, Banich MT, O'Reilly RC (2011) A unified framework for inhibitory control. Trends Cogn Sci 15(10):453–459

Obeso I, Wilkinson L, Jahanshahi M (2011) Levodopa medication does not influence motor inhibition or conflict resolution in a conditional stop-signal task in Parkinson's disease. Exp Brain Res 213:435–445

Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychol 9:97–113

Pachella RG (1974) The interpretation of reaction time in information processing research. In: Kantowitz BH (ed) Human information processing: tutorials in performance and cognition. Erlbaum, Hillsdale, pp 41–82

Praamstra P, Plat FM (2001) Failed suppression of direct visuomotor activation in Parkinson's disease. J Cogn Neurosci 13:31–43

Praamstra P, Stegeman D, Cools A, Horstink MW (1998) Reliance on external cues for movement initiation in Parkinson's disease: evidence from movement-related potentials. Brain 121:167–177

Proctor RW, Lu CH, Wang H, Dutta A (1995) Activation of response codes by relevant and irrelevant stimulus information. Acta Psychol 90:275–286

Rabbit PMA (1966) Errors and error correction in choice–response tasks. J Exp Psychol 71:264–272

Ratcliff R (1979) Group reaction time distributions and an analysis of distribution statistics. Psych Bull 86:446–461

Ridderinkhof KR (2002) Activation and suppression in conflict tasks: empirical clarification through distributional analyses. In: Prinz W, Hommel B (eds) Common mechanisms in perception and action. Attention and performance, vol 19. Oxford University Press, Oxford, pp 494–519

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

Rinkenauer G, Osman A, Ulrich R, Muller-Gethmann H, Mattes S (2004) On the locus of speed-accuracy trade-off in reaction time: inferences from the lateralized readiness potential. J Exp Psychol Gen 133:261–282

Roger C, Bénar CG, Vidal F, Hasbroucq T, Burle B (2010) Rostral Cingulate Zone and correct response monitoring: ICA and source localization evidences for the unicity of correct- and error-negativities. NeuroImage 51:391–403

Scheffers MK, Coles MG, Bernstein P, Gehring WJ, Donchin E (1996) Event-related brain potentials and error-related processing: an analysis of incorrect responses to go and no-go stimuli. Psychophysiology 33(1):42–53

Schmiedt-Fehr C, Schwendemann G, Herrmann M, Basar-Eroglu C (2007) Parkinson's disease and age-related alterations in brain oscillations during a Simon task. Neuroreport 18:277–281

Simon JR (1990) The effects of an irrelevant directional cue on human information processing. In: Proctor RW, Reeve TG (eds) Stimulus–response compatibility: an integrated perspective. Elsevier, New York, pp 31–63

Simon JR, Rudell AP (1967) Auditory S-R compatibility: the effect of an irrelevant cue on information processing. J Appl Psychol 51:300–304

Smid HGOM, Mulder G, Mulder LJM (1990) Selective response activation can begin before stimulus recognition is complete: a psychophysiological and error analysis of continuous flow. Acta Psychol 74:169–201

Staude GH (2001) Precise onset detection of human motor responses using a whitening filter and the log-likelihood-ratio test. IEEE Trans Biomed Eng 48:1292–1305

Swainson R, Rogers RD, Sahakian BJ, Summers BA, Polkey CE, Robbins TW (2000) Probabilistic learning and reversal deficits in patients with Parkinson's disease or frontal or temporal lobe lesions: possible adverse effects of dopaminergic medication. Neuropsychol 38:596–612

van den Wildenberg WP, Wylie SA, Forstmann BU, Burle B, Hasbroucq T, Ridderinkhof KR (2010) To head or to heed? Beyond the surface of selective action inhibition: a review. Front Hum Neurosci. doi:10.3389/fnhum.2010.00222

Vidal F, Hasbroucq T, Grapperon J, Bonnet M (2000) Is the 'error negativity' specific to errors? Biol Psychol 51:109–128

Vincent SB (1912) The function of vibrissae in the behavior of the white rat. Behav Monog 1(5):1–181

Winer BJ (1971) Statistical principles in experimental design. McGraw-Hill, New York

Wylie SA, Ridderinkhof KR, Elias WJ, Frysinger RC, Bashore TR, Downs KE et al (2010) Subthalamic nucleus stimulation influences expression and suppression of impulsive behavior in Parkinson's disease. Brain 133:3611–3624

Wylie SA, Claassen DO, Huizenga HM, Schewel KD, Ridderinkhof KR, Bashore TR et al (2012) Dopamine agonists and the suppression of impulsive motor actions in Parkinson's disease. J Cogn Neurosci 24:1709–17224

Yellott JL (1971) Correction for guessing and the speed-accuracy trade-off in choice reaction time. J Math Psychol 8:159–199