

# Accepted Manuscript

Acting without being in control: Exploring volition in Parkinson's disease with impulsive compulsive behaviours

Lucia Ricciardi, MD, PhD, Patrick Haggard, Lieke de Boer, Chiara Sorbera, Max-Philipp Stenner, Francesca Morgante, Mark J. Edwards



PII: S1353-8020(17)30143-8

DOI: [10.1016/j.parkreldis.2017.04.011](https://doi.org/10.1016/j.parkreldis.2017.04.011)

Reference: PRD 3288

To appear in: *Parkinsonism and Related Disorders*

Received Date: 8 December 2016

Revised Date: 14 March 2017

Accepted Date: 18 April 2017

Please cite this article as: Ricciardi L, Haggard P, de Boer L, Sorbera C, Stenner M-P, Morgante F, Edwards MJ, Acting without being in control: Exploring volition in Parkinson's disease with impulsive compulsive behaviours, *Parkinsonism and Related Disorders* (2017), doi: 10.1016/j.parkreldis.2017.04.011.

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 proof before it is published in its final 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.

## **ACTING WITHOUT BEING IN CONTROL: EXPLORING VOLITION IN PARKINSON'S DISEASE WITH IMPULSIVE COMPULSIVE BEHAVIOURS**

Lucia Ricciardi<sup>1</sup>; Patrick Haggard<sup>2</sup>; Lieke de Boer<sup>2,3</sup>; Chiara Sorbera<sup>4</sup>; Max-Philipp Stenner<sup>5</sup>; Francesca Morgante\*<sup>4</sup> and Mark J Edwards\*<sup>1</sup>

<sup>1</sup> Institute of Molecular and Clinical Sciences, St George's University of London, London, United Kingdom

<sup>2</sup>Institute of Cognitive Neuroscience, UCL, London;

<sup>3</sup>Aging Research Center, Karolinska Institute, Stockholm, Sweden;

<sup>4</sup>Department of Clinical and Experimental Medicine, University of Messina, Italy;

<sup>5</sup>Department of Neurology, Otto-von-Guericke University Hospital Magdeburg, Germany

\* These authors share senior authorship.

**Running title:** Action control in PD with ICB

**Title (character count including spaces):** 111

**Abstract count:** 241; **Word count (text):** 3275

**Tables:** 2. **Figures:** 2

**Supplementary material:** 1 supplementary material, 4 supplementary tables

**References:** 30

**Key words:** Parkinson's disease; impulse control disorders; impulsive-compulsive behaviours; sense of agency; action inhibition; reward.

**Funding sources:** None

**\*Correspondence to:**

Dr. Lucia Ricciardi, MD, PhD  
Institute of Molecular and Clinical Sciences, St George's University of London  
Cranmer Terrace, London SW17 0RE, United Kingdom  
Email: [lucia.ricciardi2@gmail.com](mailto:lucia.ricciardi2@gmail.com)

**ABSTRACT**

**Background:** Several aspects of volitional control of action may be relevant in the pathophysiology of impulsive-compulsive behaviours (ICB) in Parkinson's disease (PD). We aimed to explore multiple aspects of action control, assessing reward-related behaviour, inhibition (externally and internally triggered) and sense of agency in PD patients, with and without ICB compared to healthy subjects.

**Methods:** Nineteen PD patients with ICB (PD-ICB), 19 PD without ICB (PD-no-ICB) and 19 healthy controls (HC) underwent a battery of tests including: Intentional Binding task which measures sense of agency; Stop Signal Reaction Time (SSRT) measuring capacity for reactive inhibition; the Marble task, assessing intentional inhibition; Balloon Analog Risk Task for reward sensitivity.

**Results:** One-way ANOVA showed significant main effect of group for action binding ( $p=0.004$ ,  $F=6.27$ ). Post hoc analysis revealed that PD-ICB had significantly stronger action binding than HC ( $p=0.004$ ), and PD-no-ICB ( $p=0.04$ ). There was no difference between PD-no-ICB and HC. SSRT did not differ between PD groups, whereas a significant difference between PD-no-ICB and HC was detected ( $p=0.01$ ). No other differences were found among groups in the other tasks.

**Conclusions:** PD patients with ICB have abnormal performance on a psychophysical task assessing sense of agency, which might be related to a deficit in action representation at cognitive/experiential level. Yet, they have no deficit on tasks evaluating externally and internally triggered inhibitory control, or in reward-based decision-making. We conclude that impaired sense of agency may be a factor contributing to ICB in PD patients.

## INTRODUCTION

Impulsive compulsive behaviours (ICBs) are common neuropsychiatric complications of PD associated with dopaminergic treatment, particularly with dopamine agonists [1]. ICBs include impulse control disorders (ICD) such as pathological gambling, hypersexuality, compulsive buying and binge eating, and compulsive behaviours such as punting and compulsive use of dopamine replacement therapy (also known as dopamine dysregulation syndrome, DDS). ICDs are defined as behaviours that are performed repetitively, excessively, and compulsively to an extent that they interfere with major areas day to day functioning and have been characterised as behavioural addictions [1]. Although ICDs have been linked to the use of dopamine agonists, clinical and experimental evidence suggest that they are unlikely to be a purely drug-induced phenomenon. Current hypotheses propose an interaction between chronic administration of dopaminergic drugs and disease specific effects on the brain network involved in reward [2]. Impaired reward-reinforcement learning [3], increased impulsivity and poor self-control [4], have been demonstrated in PD with ICD. It has been hypothesized that in predisposed PD patients, dopaminergic treatment, particularly with dopamine agonists, might enhance risk-taking behavior [5,6], impair learning from negative feedback [7] and promote impulsive decision-making [8].

Although impairment of reward-related behavior plays a role in the development of ICD in PD, value-related computations are only one aspect of decision-making. Voluntary actions typically aim at bringing about some goal or outcome and successful actions are accompanied by a characteristic “sense of agency”. This refers to the subjective experience that an action and its outcome, were under one’s own voluntary control. The ability to link an external outcome to an intentional action comprises both the feeling of having initiated the action and an attribution of the outcome to one’s own action, rather than any other cause [9]. Accordingly, altered sense of agency is a feature of many neuropsychiatric conditions [10]. The temporal binding task has been proposed by Haggard and co-workers [11] as an implicit marker of sense of agency. In the binding task, subjects make judgements about the perceived time of actions and of tones that follow the voluntary action. Intentional actions are perceived to occur later in time and their effects (i.e. tones) are perceived to occur earlier in time compared to their respective baseline conditions in which the action occurs without the subsequent tone, or the tone occurs without being triggered by any action. Importantly, this temporal attraction between self generated actions and their outcomes was absent when the voluntary action was replaced

by an involuntary movement. For this reason, the ‘intentional binding effect’ has been suggested to be a quantitative yet implicit index of awareness of action or agency [9,11].

The ability to inhibit an action is a further fundamental aspect of voluntary control. Many classical experimental paradigms involve preparing an action, but then withholding it in response to an external signal (e.g. stop signal reaction time tasks). However, the capacity to decide *internally* to inhibit an action, in the absence of any external instruction, is arguably more important for self-control. Internally driven action inhibition is difficult to assess experimentally. One cognitive model of action control [12] hypothesises a ‘*whether decision*’, distinct from decisions about what action to make, and when to make it. The “whether decision” could trigger a process of intentional inhibition of actions that have been prepared, but should now be withheld. Experimental paradigms to probe this aspect of internal action inhibition have been proposed [13].

Our aim was to perform a comprehensive assessment of voluntary control of action with assessments of sense of agency, action inhibition (both internally and externally triggered) and reward-related decision-making in PD patients with and without ICB compared to a control group of healthy participants.

## METHODS

Thirty-eight PD patients were included in the study. Inclusion criteria were: a diagnosis of PD according to UK Parkinson’s Disease Society Brain Bank criteria; treatment and clinical condition stable for at least 4 weeks prior to the study. Exclusion criteria were: any major concurrent neurological or psychiatric disorders; a score < 25 on the Montreal Cognitive Assessment (MOCA). The sample of patients included: 19 PD patients without ICB (PD-no-ICB) and 19 PD patients with ICB (PD-ICB). A semi-structured interview using accepted diagnostic criteria[14] for pathological gambling, compulsive buying, compulsive sexual behaviour, binge eating, punting and DDS (anytime in the past 6 months) was employed to reach the diagnosis of each of these ICB. Accordingly, among PD-ICB patients, one had an isolated ICD (hypersexuality), all the remaining patients presenting at least 2 ICB (pathological gambling = 4, compulsive sexual behaviour = 12, compulsive shopping = 11, binge eating = 8, punting = 11, DDS = 3). All ICB patients reported ICD. Nineteen healthy control subjects (HC) (matched for age, gender and education level) were also recruited as a control group. Individuals with a history of any major concurrent neurological or psychiatric disorders were excluded. Patients and HC gave written,

informed consent. Institutional ethics approval was obtained and the experiment was conducted in accordance with the Declaration of Helsinki.

The following variables were retrieved: educational level, age at study entry, age at disease onset, disease duration. Levodopa and dopamine-agonist use (D-Ag) equivalent daily dose (LEDD) was calculated [15]. Disease severity and stage were respectively rated by means of the Unified Parkinson's Disease Rating Scale and the Hoehn and Yahr scale. The questionnaire for impulsive-compulsive disorders in Parkinson's disease (QUIP-RS)[16] was employed to evaluate severity of ICB. All patient were tested in their "best ON" state (the best motor state at peak effect after taking their usual medication dose). Beck Depression Inventory (BDI), Hamilton Anxiety Rating Scale (HAM-A), Apathy Evaluation Scale (AES) were employed to rate respectively depression, anxiety and apathy. Besides testing of overall cognitive function by means of the MOCA, all subjects underwent the following battery of tests for specific cognitive functions: (1) working memory: digit span forward and backward; 2) executive functions and attention: phonological word fluency; categorical word fluency; Trail Making Test A and B; 3) and visuo-spatial attention: Matrix Cancellation Features Target (MCFT).

For the psychophysical study, we used a test battery developed to assess key cognitive components of the control of voluntary action. This test battery includes measures of: 1) sense of agency by the Temporal Binding task (TB)[16]; 2) inhibition by the Stop signal reaction time task (SSRT)[17]; 3) intentional stopping by the Marble Task (modified version of the task by Schel et al.[18]).4) decision making under risk: Balloon Analogue Risk Task (BART) (modified version of the task by Lejuez et al[19]).

Specific details of each test are given in Supplementary material online. Figure 1 illustrates the study design.

## STATISTICAL ANALYSIS

Demographical data were compared across the 3 groups (PD-ICB, PD-no-ICB, HC) using the Kruskal-Wallis test. Two-groups comparisons (HC vs PD and PD-ICB vs PD-no-ICB) were computed for all clinical, psychiatric and cognitive variables by means of Mann-Whitney U test. Behavioural findings were compared across different groups (PD-ICB, PD-no-ICB, HC) by means of one-way analysis of variance (ANOVA) with "group" as dependent variable.

Correlational analysis was conducted using Spearman bivariate correlations. To control for potential underlying causes of differences in action binding in the patients groups we

conducted a multiple linear regression analysis where action binding was the dependent variable and group (dummy-coded ICB/no-ICB), disease duration, medication (LEDD), BDI, HARS and AES were the regressors. Statistical analysis was performed by software program SPSS-21 (SPSS Inc; Chicago, IL, USA). Data are shown as mean values  $\pm$  standard deviations. Significance level was set at  $p < 0.05$  unless differently specified.

## RESULTS

The three groups did not differ for age, education level and gender distribution. Mann-Whitney U tests revealed that PD-ICB had significantly longer disease duration than PD-no-ICB and had a higher total LEDD; however, D-Ag LEDD did not differ between the two groups. No other significant difference was found between the two PD groups (table 1).

Compared to HC, PD patients reported more severe depression, anxiety and apathy. Only apathy was more pronounced in the PD-ICB group compared to PD-no-ICB. Global cognitive function as per MOCA was comparable between HC and PD and between PD-ICB and PD-no-ICB. When evaluating specific cognitive domains, PD had lower scores compared to HC in tests evaluating working memory (digit span forward), attentive/executive functions (digit span backward, phonological fluency, semantic fluency, TMT-A), and attentional visual conjunction search (MFCT). However, no difference in any cognitive domain was detected between PD-no-ICB and PD-ICB (supplementary table 1).

Results from psychophysical testing are shown in Table 2. For action binding, one-way ANOVA showed a significant main effect of group due to a significant difference between PD-ICB and HC ( $p=0.004$ ) and PD-ICB and PD-no-ICB ( $p=0.04$ ), by post-hoc t-test (Figure 2). PD-no-ICB and HC were not different ( $p=1$ ). No significant difference among groups was found for tone binding. Given that PD-ICB and PD-no-ICB differed by disease duration and total LEDD, we conducted a one-way analysis of covariance (ANCOVA) to compare the performance of the two PD groups on each psychophysical task taking into account these variables. Although groups were matched for LEDD dopamine-agonists, we added this variable as a covariate in the ANCOVA analysis in order to control for a potential impact of therapy variability on the behavioural findings. After adjusting for disease duration, LEDD dopamine-agonists and total LEDD, one-way ANCOVA showed that the group effect on action binding remained significant ( $F=5.2$ ;  $p=0.028$ ; partial eta squared value of 0.1), either when co-varying for disease duration only ( $F=5.3$ ;  $p=0.03$ ), for total LEDD only ( $F=6.2$ ,  $p=0.02$ ) or for LEDD dopamine-agonists only ( $F=4.0$ ;  $p=0.05$ ). We also compared the standard deviations across repeated trials of time estimates in each

condition, as a measure of perceptual timing abilities. Inconsistent time estimation, for example due to poor attention, would produce high standard deviation of timing estimates across trials. However, we found no significant difference among groups for baseline action, baseline tone, operant action and operant tone conditions. This finding excludes the possible effect of differences among groups in temporal judgement abilities, which might have influenced the results.

One-way ANOVA showed a significant main effect of group in 50% quantile SSRT. This was due to impaired stopping ability in PD-no-ICB ( $p=0.01$ ) but not in PD-ICB ( $p=0.3$ ) compared to HC. PD groups did not differ in the quantile SSRT ( $p=0.1$ ). However, after adjusting for disease duration and total LEDD, one-way ANCOVA showed that the group effect on the 50% quantile SSRT was no longer significant ( $F=2.7$ ;  $p=0.1$ ).

One-way ANOVA showed no difference between groups in each of the measures of the Marble task and the BART (Table 2). One-way ANOVA showed a significant difference among groups in terms of number of green marbles missed in the Marble Task ( $p=0.01$ ,  $F$  4.9; Table 2). However, after controlling for differences in disease duration, total LEDD and LEDD dopamine-agonists (one-way ANCOVA) there was no significant difference among groups for this variable and for any of the other variables in the Marble task and the BART. Thus differences between groups on these tasks might reflect variation in medication use and disease duration, rather than a pure effect of ICB.

Spearman's bivariate correlations, were conducted in each group separately (PD and HC groups) to examine the relation between binding task measures and the other psychometric variables (i.e., BDI, HARS, AES). This revealed a significant correlation in the overall PD group between anxiety by HARS score and tone binding and between total LEDD and tone binding. Spearman rank correlation analysis in the PD-ICB group demonstrated a significant correlation between total LEDD and tone binding ( $r=0.5$ ,  $p=0.01$ ). No significant correlation was found between D-Ag LEDD, BDI, HARS, AES, disease duration (Supplementary table 2) or QUIP-RS (Supplementary table 3) and any measure of the psychophysical tasks after correcting for multiple comparisons.

Multiple linear regression with action binding as dependent variable and BDI, HARS, AES, disease duration, LEDD and patient groups (dummy-coded ICB/nonICB) as regressors showed that ICB was a significant predictor of action binding performance ( $b=0.4$ ,  $SE=27.8$ ,  $p=0.03$ , 95% CI [4.7, 118.5]) after controlling for affective, cognitive and disease related factors (Supplementary table 4).



## DISCUSSION

Our results show that PD patients with ICB have abnormally strong binding in the perceived time of an action towards its subsequent outcome, compared to both PD patients without ICB and to healthy subjects. In contrast, we could not find any differences in tasks evaluating externally and internally triggered inhibition, or in risk/reward-based decision-making. The strength of this study is that we have explored several domains relevant to action control in patients with Parkinson's disease with and without ICB, using a broad range of psychomotor tasks. The tasks assessed reward-related behaviour, inhibition (externally and internally triggered) and sense of agency. Specifically, we employed the intentional binding task as a marker of sense of agency for voluntary action. The pairing of an outcome (a tone) with a self-paced action alters the perceived timing of these events compared to judgements of timing of action or a tone occurring alone. The temporal attraction or "binding" between self-generated actions and their outcomes has been suggested to be a quantitative index of awareness of action or agency [9]. In healthy people the "binding" effect is asymmetric, in that it is strongest for the perceived timing of the tone which is perceived to move back in time towards the time of the action more than the perceived timing of the action moves towards the time of the tone. This asymmetry is often interpreted in terms of optimal integration between action and tone events [20], with each event attracting the other in proportion to its perceptual saliency.

A novel finding of our study demonstrates that PD-ICB have an abnormally large shift in perceived timing of the action *towards* the tone, compared to PD without ICB and healthy subjects. The intentional binding paradigm was already tested by Moore and co-workers in nine PD patients On and Off medication, but ICB status was not investigated [10]. In that study, the typical asymmetry of the binding effect was evident in PD Off medication similarly to PD-no-ICB in our sample, whereas levodopa seemed to enhance action binding in PD [10]. In our analysis, PD-ICB maintained a stronger action binding than PD-no-ICB, also after adjusting for total LEDD and disease duration; moreover, the two patient groups did not differ by UPDRS-III or Hoen-Yahr stage, although we have to acknowledge that activity of daily living (by UPDRS-II) and complications of therapy (by UPDRS IV) were more pronounced in PD-ICB, although not significantly. This supports the view that a larger shift in action-binding specifically may be related to ICB rather than to dopaminergic treatment or disease severity and duration.

Our results suggest that agency may be weakened in patients with PD-ICB because of a disturbance in perceptual processing that causes actions to be more strongly attracted

towards outcomes. However, we cannot determine whether the altered perceptual salience predominantly affects actions or outcomes in ICB patients. An abnormally strong representation of the outcome should have made patients adjust their behaviour on the BART task, making them more sensitive to the effect of risk level and its effect on outcome. As we did not find any difference between groups in risk-taking on the BART, we propose that an abnormally weak representation of action in ICB is the explanation for the increased action binding.

The lack of functional neuroimaging in our study does not allow us to define the neural networks underlying increased action binding in ICB patients but we hypothesize a central role for pre-supplementary motor area (SMA) based on previous experimental studies [21, 22]. Indeed, increased action binding has been found also in the most affected hand of patients with cortical basal syndrome (CBS) and was correlated to the severity of alien limb and apraxia as well to structural and functional changes in pre-SMA and in its connections to prefrontal cortex [21]. The greater motor severity of CBS coupled with high-level sensory deficits and apraxia [21] might explain why CBS with alien limb phenomena can produce complete loss of agency attribution (“it isn’t me moving my hand”). On the other side, PD-ICB attribute the action to themselves, but the subjective experience of volition associated with the action itself is weak (“I know I am acting but I don’t know what I’m doing”).

Our result cannot readily be explained by deficits in reward-related decision-making, as our binding task was valence-free. Previous functional neuroimaging studies have reported changes in reward-associated areas in PD with ICD, interpreted as a result of increased sensitivity of reward-related areas to dopamine-agonists [23-24]. Our data do not contradict these studies, as we only evaluated one component of reward-related decision-making, namely risk-taking behaviour. However, we rather suggest that other mechanisms may also contribute to the pathophysiology of ICB, in addition to the well-known effect on valence. For example, the importance of dopamine transmission for salience processing has also been emphasised in recent accounts of psychosis [25]. Further, though salience and valence are highly correlated, they do involve partially dissociable networks. These networks overlap in key areas such as the ventral striatum, which is known to be important in the pathophysiology of PD and the mechanism of action of dopaminergic medication.

ICB patients did not differ from healthy volunteers nor from patients without ICB in the BART task of decision-making, and specifically of risk-taking. The inconsistency of

previous literature on risk-taking behaviour in PD-ICB may be due to methodological differences, driven by different tasks employed (BART, Iowa Gambling Task, other gambling tasks), different clinical characteristics of patients or different pharmacological conditions (“On” or “Off” medication) [6,7,26-28]. Yet, our data are in line with previous studies showing no difference in the BART between PD patients with and without ICB tested “On” medication [27] or both “On” and “Off” [6]. However, in the study by Claassen and co-workers [6], only PD-ICB patients tended to increase risk-taking during “On” compared to “Off” state [6].

We also evaluated measures of reactive and voluntary inhibition demonstrating that patients with and without ICB performed similarly in both externally-triggered inhibition (SSRT) and internally triggered inhibition tasks (Marble Task). Patients with PD have previously been reported to be impaired in the SSRT, a task used as a measure of reactive inhibition which is not modified by dopaminergic medication [29]. In our study, a longer SSRT was demonstrated in the PD-no-ICB group compared to HC, although post-hoc analysis did not show differences between PD-ICB and PD-no-ICB. The SSRT results are in line with previous studies showing no differences between patients with and without ICB in other tasks assessing reactive inhibitory control, including the Stroop test [30] and a go/no-go task [5]. Our results also suggest that the “whether” component of action control tested by the Marble Task is unaffected by PD itself or the presence of ICB.

We acknowledge limitations to our study, including the lack of evaluation of the role of dopaminergic drugs (patients were tested only ‘On’ medication). However, this is the most real day-to-day life condition, since patients are usually on treatment in everyday life; moreover, the binding effect remained significant when correcting for LEDD. Additionally, given the lack of functional neuroimaging, we can only speculate on the neural basis of the behavioural effects observed in this study.

In conclusion, our data provide some support for the hypothesis that agency in ICB is impaired as a result of an abnormally weak representation of action, such that actions are more readily captured by outcomes. If the normal regulatory signals for action are weak or absent, then specific salient outcomes could “capture” behaviour, resulting in actions occurring without a strong experience of endogenous voluntary control. This finding contributes to the pathophysiology of ICB in PD, in addition to previously reported deficits in reward-related action control. Our finding of altered experience of volition opens new perspectives on future therapeutic management of ICB.

**FIGURES LEGEND**

**Figure 1. Study design.** The psychophysiological battery included tests evaluating the sense of agency (temporal binding task, panel A-C), motor stopping (Stop signal reaction time, panel D), intentional inhibition (modified version of the Marble task, panel E) and decision-making under risk (Balloon Analogue Risk Task, panel F). See text for details and references for each single task.

**Figure 2. Action binding in PD according to ICB status.** Parkinson's disease (PD) patients with impulsive compulsive behaviours (ICB) showed a significantly stronger action binding than healthy controls ( $p=0.004$ ), and patients without ICB ( $p=0.04$ ). There was no difference between patients without ICB and healthy controls. Tone binding and overall binding did not differ among the three groups.

**CONTRIBUTORS:** LR, LdB and CS carried out data collection. LR and LdB carried out data analysis. LR and MPS carried out statistical analysis. LR, PH, FM and MJE designed the study. LR, PH, LdB, CS, MPS, FM, MJE drafted and revised the manuscript.

**COMPETING INTERESTS:**

**Dr. Francesca Morgante** receives royalties from publication of Disorders of Movement (Springer 2016). She was part of advisory boards of Medtronic and Chiesi farmaceutici. She has received honoraria for speaking from UCB Pharma, Medtronic, Lundbeck, Chiesi, Abbvie, Allergan, Merz.

**Professor Mark J Edwards** receives royalties from publication of Oxford Specialist Handbook Of Parkinson's Disease and Other Movement Disorders (Oxford University Press, 2008) and receives research support from a National Institute for Health Research (NIHR) grant where he is the PI. He has received honoraria for speaking from UCB.

**The other authors** do not report any disclosures.

## REFERENCES

- [1] D. Weintraub, A.S. David, A.H. Evans, J.E. Grant, M. Stacy. Clinical spectrum of impulse control disorders in Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society* 30(2) (2015) 121-7.
- [2] R. Cilia, T. van Eimeren. Impulse control disorders in Parkinson's disease: seeking a roadmap toward a better understanding. *Brain Struct.Funct.* 216(4) (2011) 289-299.
- [3] M.J. Frank, L.C. Seeberger, R.C. O'reilly. By carrot or by stick: cognitive reinforcement learning in parkinsonism. *Science* 306(5703) (2004) 1940-1943.
- [4] I.U. Isaias, C. Siri, R. Cilia, D. De Gaspari, G. Pezzoli, A. Antonini. The relationship between impulsivity and impulse control disorders in Parkinson's disease. *Mov Disord.* 23(3) (2008) 411-415.
- [5] M. Rossi, E.R. Gerschovich, D. de Achaval, S. Perez-Lloret, D. Cerquetti, A. Cammarota, M. Ines Nouzeilles, R. Fahrner, M. Merello, R. Leiguarda. Decision-making in Parkinson's disease patients with and without pathological gambling. *European journal of neurology* 17(1) (2010) 97-102.
- [6] D.O. Claassen, W.P. van den Wildenberg, K.R. Ridderinkhof, C.K. Jessup, M.B. Harrison, G.F. Wooten, S.A. Wylie. The risky business of dopamine agonists in Parkinson disease and impulse control disorders. *Behavioral neuroscience* 125(4) (2011) 492-500.
- [7] A. Djamshidian, A. Jha, S.S. O'Sullivan, L. Silveira-Moriyama, C. Jacobson, P. Brown, A. Lees, B.B. Averbeck. Risk and learning in impulsive and nonimpulsive patients with Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society* 25(13) (2010) 2203-10.
- [8] A. Djamshidian, S.S. O'Sullivan, Y. Sanotsky, S. Sharman, Y. Matviyenko, T. Foltynie, R. Michalczuk, I. Aviles-Olmos, L. Fedoryshyn, K.M. Doherty, Y. Filts, M. Selikhova, H. Bowden-Jones, E. Joyce, A.J. Lees, B.B. Averbeck. Decision making, impulsivity, and addictions: do Parkinson's disease patients jump to conclusions? *Movement disorders : official journal of the Movement Disorder Society* 27(9) (2012) 1137-45.
- [9] P. Haggard, V. Chambon. Sense of agency. *Current biology : CB* 22(10) (2012) R390-2.
- [10] J.W. Moore, S.A. Schneider, P. Schwingenschuh, G. Moretto, K.P. Bhatia, P. Haggard. Dopaminergic medication boosts action-effect binding in Parkinson's disease. *Neuropsychologia* 48(4) (2010) 1125-32.
- [11] P. Haggard, S. Clark, J. Kalogeras. Voluntary action and conscious awareness. *Nat.Neurosci.* 5(4) (2002) 382-385.
- [12] M. Brass, P. Haggard. The what, when, whether model of intentional action. *The Neuroscientist : a review journal bringing neurobiology, neurology and psychiatry* 14(4) (2008) 319-25.
- [13] S. Kuhn, P. Haggard, M. Brass. Intentional inhibition: how the "veto-area" exerts control. *Hum.Brain Mapp.* 30(9) (2009) 2834-2843.
- [14] D. Weintraub, S. Hoops, J.A. Shea, K.E. Lyons, R. Pahwa, E.D. Driver-Dunckley, C.H. Adler, M.N. Potenza, J. Miyasaki, A.D. Siderowf, J.E. Duda, H.I. Hurtig, A. Colcher, S.S. Horn, M.B. Stern, V. Voon. Validation of the questionnaire for impulsive-compulsive disorders in Parkinson's disease. *Mov Disord.* 24(10) (2009) 1461-1467.

- [15] C.L. Tomlinson, R. Stowe, S. Patel, C. Rick, R. Gray, C.E. Clarke. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Mov Disord.* 25(15) (2010) 2649-2653.
- [16] D. Weintraub, E. Mamikonyan, K. Papay, J.A. Shea, S.X. Xie, A. Siderowf. Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale. *Mov Disord.* 27(2) (2012) 242-247.
- [17] G.P. Band, M.W. van der Molen, G.D. Logan. Horse-race model simulations of the stop-signal procedure. *Acta psychologica* 112(2) (2003) 105-42.
- [18] M.A. Schel, D.A. Windhorst, M.W. van der Molen, E.A. Crone. Developmental change in intentional action and inhibition: a heart rate analysis. *Psychophysiology* 50(8) (2013) 812-9.
- [19] C.W. Lejuez, J.P. Read, C.W. Kahler, J.B. Richards, S.E. Ramsey, G.L. Stuart, D.R. Strong, R.A. Brown. Evaluation of a behavioral measure of risk taking: the Balloon Analogue Risk Task (BART). *J.Exp.Psychol.Appl.* 8(2) (2002) 75-84.
- [20] J.W. Moore, S.S. Obhi. Intentional binding and the sense of agency: a review. *Consciousness and cognition* 21(1) (2012) 546-61.
- [21] N. Wolpe, J.W. Moore, C.L. Rae, T. Rittman, E. Altena, P. Haggard, J.B. Rowe. The medial frontal-prefrontal network for altered awareness and control of action in corticobasal syndrome. *Brain* 137(Pt 1) (2014) 208-20.
- [22] J.W. Moore, D. Ruge, D. Wenke, J. Rothwell, P. Haggard. Disrupting the experience of control in the human brain: pre-supplementary motor area contributes to the sense of agency. *Proc Biol Sci* 277(1693) (2010) 2503-9.
- [23] T. van Eimeren, B. Ballanger, G. Pellecchia, J.M. Miyasaki, A.E. Lang, A.P. Strafella. Dopamine agonists diminish value sensitivity of the orbitofrontal cortex: a trigger for pathological gambling in Parkinson's disease? *Neuropsychopharmacology* 34(13) (2009) 2758-2766.
- [24] K. Wu, M. Politis, S.S. O'Sullivan, A.D. Lawrence, S. Warsi, S. Bose, A.J. Lees, P. Piccini. Single versus multiple impulse control disorders in Parkinson's disease: an (1)(1)C-raclopride positron emission tomography study of reward cue-evoked striatal dopamine release. *J Neurol* 262(6) (2015) 1504-14.
- [25] S. Kapur. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *The American journal of psychiatry* 160(1) (2003) 13-23.
- [26] V. Voon, B. Reynolds, C. Brezing, C. Gallea, M. Skaljic, V. Ekanayake, H. Fernandez, M.N. Potenza, R.J. Dolan, M. Hallett. Impulsive choice and response in dopamine agonist-related impulse control behaviors. *Psychopharmacology (Berl)* 207(4) (2010) 645-59.
- [27] H. Rao, E. Mamikonyan, J.A. Detre, A.D. Siderowf, M.B. Stern, M.N. Potenza, D. Weintraub. Decreased ventral striatal activity with impulse control disorders in Parkinson's disease. *Mov Disord.* 25(11) (2010) 1660-1669.
- [28] A.R. Bentivoglio, E. Baldonero, L. Ricciardi, F. De Nigris, A. Daniele. Neuropsychological features of patients with Parkinson's disease and impulse control disorders. *Neurol.Sci.* 34(7) (2013) 1207-1213.

[29] I. Obeso, L. Wilkinson, M. Jahanshahi. Levodopa medication does not influence motor inhibition or conflict resolution in a conditional stop-signal task in Parkinson's disease. *Experimental brain research* 213(4) (2011) 435-45.

[30] A. Djamshidian, S.S. O'Sullivan, A. Lees, B.B. Averbeck. Stroop test performance in impulsive and non impulsive patients with Parkinson's disease. *Parkinsonism & related disorders* 17(3) (2011) 212-4.

ACCEPTED MANUSCRIPT



**Table 1: Demographic and clinical data in healthy controls (HC) and in Parkinson's disease patients (PD) with and without impulsive compulsive behaviours (ICB)**

	HC	PD-no-ICB	PD-ICB	p-values
Sample (n)	19	19	19	-
Age (years)	52.6 (7.4)	56.9 (8.4)	53.6 (9.3)	$p=0.3$
Gender (male)	8	11	12	$p=0.4$
Education level (yrs)	15.1 (1.9)	13.2 (4.60)	12.8 (3.7)	$p=0.1$
Disease duration (years)	-	<b>5.4 (2.5)</b>	<b>7.8 (4.1)</b>	<b><math>p=0.008^*</math></b>
LEDD total (mg)	-	<b>544.9 (344.5)</b>	<b>790.0 (264.6)</b>	<b><math>p=0.02^*</math></b>
LEDD D-ag (mg)	-	127.5 (143.8)	196.6 (167.9)	$p=0.2$
HY	-	<b>1.5 (0.4)</b>	<b>1.6 (0.5)</b>	<b><math>p=0.6</math></b>
UPDRS	<i>UPDRS-I</i>	-	1.6 (1.5)	$p=0.2$
	<i>UPDRS-II</i>	-	5.4 (3.8)	$p=0.07$
	<i>UPDRS-III</i>	-	12.2 (7.4)	$p=0.2$
	<i>UPDRS-IV</i>	-	2.5 (3.2)	$p=0.07$
ICB	<i>Pathological Gambling</i>	0	0	4
	<i>Hypersexuality</i>	0	0	12
	<i>Compulsive shopping</i>	0	0	11
	<i>Binge eating</i>	0	0	8
	<i>Hobbyism/punding</i>	0	0	11
	<i>DDS</i>	0	0	3

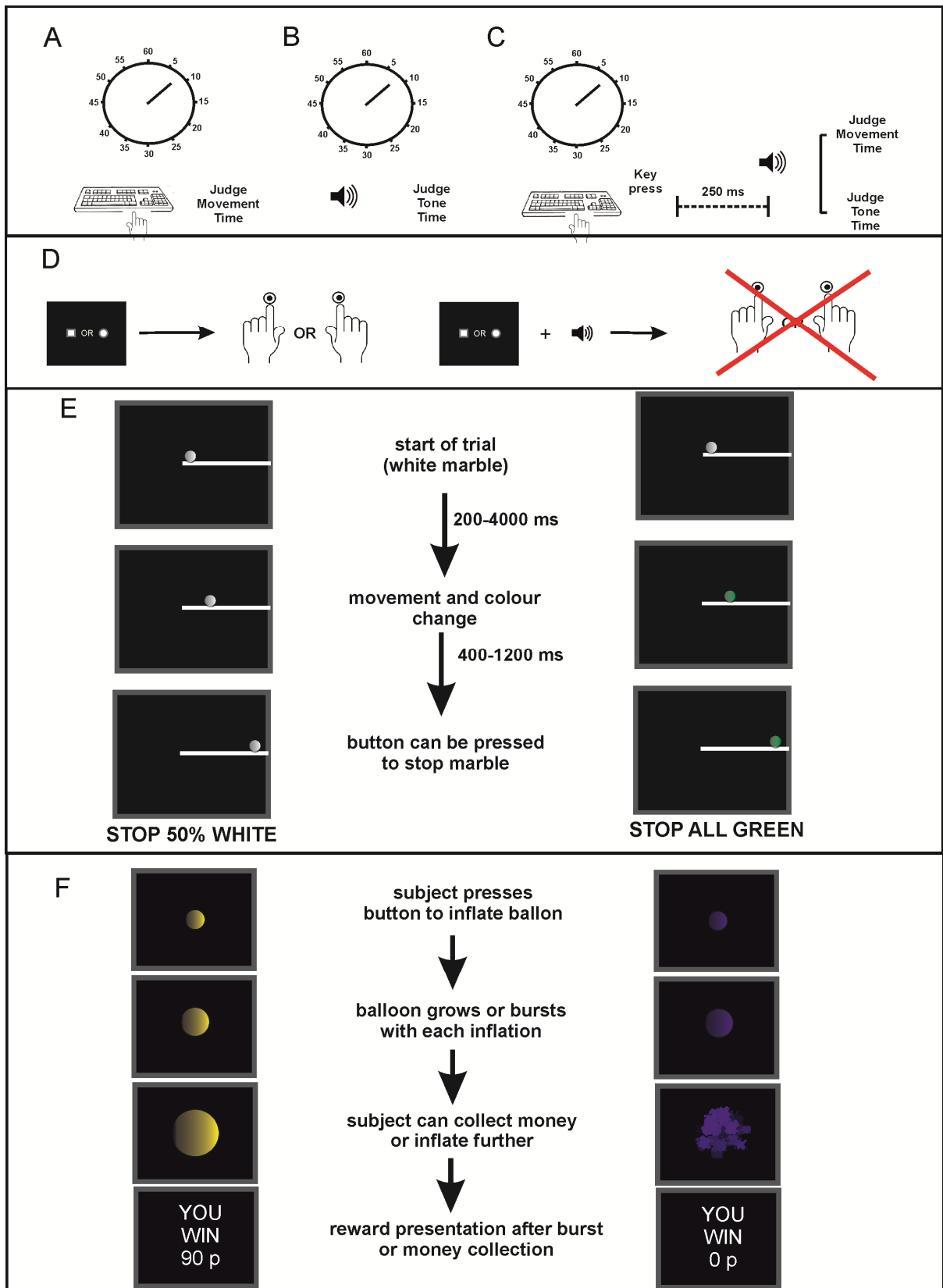
HY = Hoehn-Yahr stage; LEDD = levodopa equivalent daily dose; UPDRS = Unified Parkinson's disease rating scale (UPDRS); DDS = dopamine dysregulation syndrome.

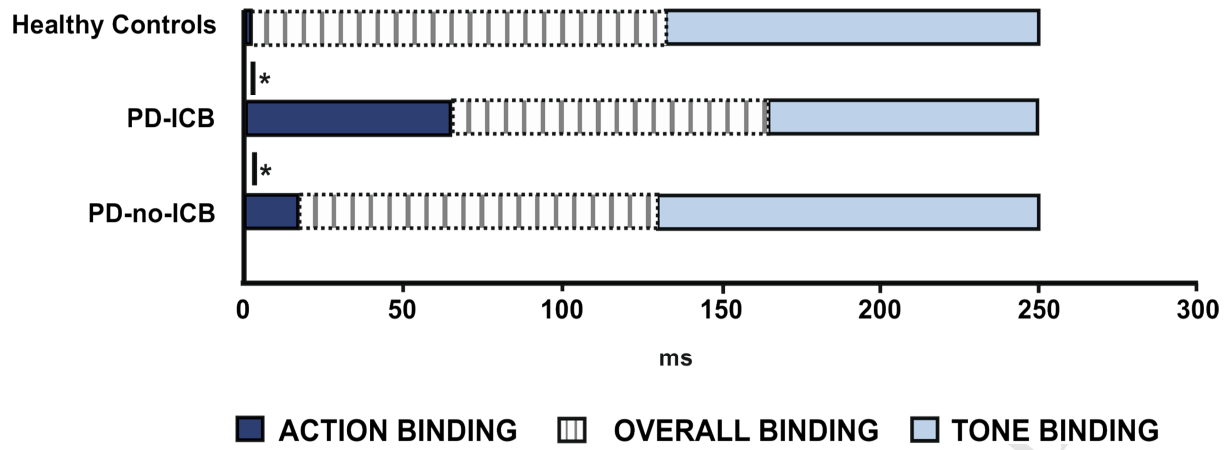
Values are means  $\pm$  Standard deviation. Comparisons were made by Mann-Whitney U test or chi-square test (for categorical data). Values in bold indicate significant differences ( $p < 0.05$ ).

**Table 2: Binding task, SSRT, Marble Task and BART in healthy controls (HC) and Parkinson's disease (PD) according to the presence of impulsive-compulsive behaviour (ICB)**

		HC	PD-no-ICB	PD-ICB	F <sub>(2,54)</sub> p-value
TJE (ms)	<i>Action (Baseline)</i>	-28 ± 50	-45 ± 51	-18 ± 47	F = 1.5, p = 0.2
	<i>Tone (Baseline)</i>	-34 ± 46	-53 ± 55	-52 ± 85	F = 0.5 p = 0.6
	<i>Action (Operant)</i>	-27 ± 46 *	-28 ± 56 *	47 ± 80 *	<b>F = 9.1</b> <b>p &lt; 0.001</b>
	<i>Tone (Operant)</i>	-152 ± 90	-173 ± 77	-137 ± 92	F = 0.8 p = 0.4
Binding (mean shift of TJE from baseline, ms)	<i>Action (ms)</i>	1 ± 39 *	17 ± 62 *	65 ± 68 *	<b>F = 6.3</b> <b>p = 0.004</b>
	<i>Tone (ms)</i>	-118 ± 86	-120 ± 82	-85 ± 96	F = 0.9 p = 0.4
SSRT	<i>Quantile SSRT (ms)</i>	<b>230.1 ± 77.1</b>	<b>312.9 ± 102.5</b>	<b>261.5 ± 94.1</b>	<b>F<sub>(2,51)</sub> = 3.6</b> <b>P = 0.03</b>
	<i>Stopped</i>	0.6 ± 0.1	0.5 ± 0.1	0.6 ± 0.05	P <sub>(2,51)</sub> = 0.1, F = 1.9
	<i>Reversal</i>	16.8 ± 4.9	17.2 ± 4.3	17.9 ± 2.9	P <sub>(2,51)</sub> = 0.7, F = 0.4
	<i>Post error slowing</i>	50.9 ± 78.9	47.2 ± 68.7	71.7 ± 77.5	P <sub>(2,51)</sub> = 0.6, F = 0.6
Marble Task	<i>RT white (ms)</i>	320.8 ± 98.2	367.9 ± 143.2	337.1 ± 69.8	P = 0.4, F = 0.9
	<i>RT green (ms)</i>	285.5 ± 51.9	322.8 ± 74.5	312.9 ± 59.8	P = 0.2, F = 1.8
	<i>White stopped</i>	0.5 ± 0.1	0.5 ± 0.2	0.6 ± 0.1	P = 0.6, F = 0.5
	<i>Green missed</i>	<b>0.3 ± 0.1</b>	<b>0.4 ± 0.2</b>	<b>0.5 ± 0.1</b>	<b>P = 0.01, F = 4.9</b>
BART	<i>Inflation low risk</i>	3.4 ± 1.3	2.9 ± 1.1	3.2 ± 0.9	P = 0.3, F = 1
	<i>Inflation high risk</i>	2.1 ± 0.6	2.1 ± 0.5	2.2 ± 0.5	P = 0.8, F = 0.2
	<i>Risk adjustment</i>	1.4 ± 0.9	0.8 ± 0.8	0.9 ± 0.9	P = 0.1, F = 1.9

BART = Balloon Analog Risk Task for reward sensitivity; SSRT = Stop Signal Reaction Time; RT = reaction time; TJE = Temporal Judgment Error. F and p-values refer to one-way factorial ANOVA with group as dependent variable (p < 0.05). \* Two HC were excluded from the analysis due to negative SSRT values. Values are means ± Standard deviation.





- We assessed the relationship between impulsive-compulsive behavior (ICB) and action control in PD.
- PD-ICB have abnormally strong action binding.
- This effect remained significant when correcting for disease duration and LEDD
- The abnormality of action binding suggests that impaired sense of agency is related to ICB in PD.