Journal of Advanced Research 8 (2017) 713–716

Contents lists available at ScienceDirect

Journal of Advanced Research

journal homepage: www.elsevier.com/locate/jare

Case Report

Impulse control disorder and response-inhibition alterations in Parkinson's disease. A rare case of totally absent functionality of the medial-prefrontal cortex and review of literature

Sara Palermo [a], Rosalba Morese [b,c,*], Maurizio Zibetti [a], Francesca Dematteis [a], Stefano Sirgiovanni [d], Mario Stanziano [d], Maria Consuelo Valentini [d], Leonardo Lopiano [a]

[a] Department of Neuroscience, University of Turin, Via Cherasco 15, 10126 Turin, Italy
[b] Department of Psychology, University of Turin, Via Verdi 10, 10123 Turin, Italy
[c] Faculty of Communication Sciences, Università della Svizzera Italiana, Via Buffi 13, CH-6904, Lugano, Switzerland
[d] Azienda Ospedaliera Universitaria "Città della Salute e della Scienza di Torino", Department of Neuroradiology, Corso Bramante 88/90, 10126 Turin, Italy

ARTICLE INFO

Article history:
Received 3 April 2017
Revised 20 September 2017
Accepted 21 September 2017
Available online 21 September 2017

Keywords:
Parkinson's disease
ICD
Response-inhibition
Action monitoring
fMRI
ACC

ABSTRACT

This report illustrates a Parkinson's disease (PD) patient with impulse-control disorder (ICD) and selective impairment in response-inhibition abilities as revealed by the performance in a functional magnetic resonance imaging (fMRI) anterior cingulate cortex - sensitive GO-NOGO task. In line with hypothesis on the role of response-inhibition disabilities in the arising of impulsivity in PD, the patient completely failed the GO-NOGO task. Moreover, fMRI acquisition revealed absent task-sensitive activity in the anterior cingulate cortex, medial prefrontal, and orbitofrontal cortices for the contrast NOGO versus GO, which signifying that a hypo-function of this network could be associated with ICD. A fronto-striatal and cingulo-frontal dysfunction may reflect impairment in metacognitive-executive abilities (such as response-inhibition, action monitoring, and error awareness) and promote compulsive repetition of behavior. Response-inhibition tasks may be useful in PD post-diagnostic phase, to better identify individuals at risk of developing ICD with dopaminergic medication.

Introduction

Parkinson's disease (PD) is the second most prevalent neurodegenerative disease in the world. PD is characterized by resting tremor, bradykinesia, rigidity, postural instability. Secondary motor symptoms could be freezing of gait, micrographia, mask-like expression and unwanted accelerations. PD can also be associated with neurobehavioral disorders, cognitive impairment, and autonomic dysfunctions. Functional changes in basal ganglia circuitry are responsible for the major clinical features of PD. Core structures of the basal ganglia are the striatum and globus pallidus, which have close functional associations with the subthalamic nucleus, substantia nigra and ventral thalamic nuclei. Indeed, a fronto-striatal network disruption affects motor and non-motor dysfunctions in PD [1]. The loss of dopaminergic neurons impacts on the functioning of four fronto-striatal circuits involved in different motor, cognitive, affective, and motivational aspects of behavior: the supplementary motor area, the dorsolateral prefrontal, the orbitofrontal, and the anterior cingulate loops. Each of them arises from a specific region of the frontal cortex and innervates different levels of the striatum before being relayed back to its cortical origin, via the thalamus [2]. The subthalamic nucleus (STN) has been regarded as a significant modulator of basal ganglia output and it has been studied because of its dual role in movement and in non-motor behaviors. In particular, the STN has been implicated in impulse control and related construct of valence processing [3]. STN transmits to two fronto-striatal circuits of particular interest with regard to non-motor symptomatology in PD: (i) the orbito-frontal cortex (OFC), associated with decision-making, impulse control, mood expression and perseveration; (ii) the anterior cingulate cortex (ACC), associated with conflict monitoring, intention, response initiation/inhibition [1]. Dopamine replacement treatment and dopamine-agonists have been implicated in impulse-control disorder (ICD) development, since they can induce alterations in those fronto-striatal networks that manage reward and mediate impulse monitoring and control [4]. Indeed, tonic stimulation of dopamine receptors may damage inhibitory control mechanisms and reward processing, while promoting compulsive repetition of behavior [4]. Voon et al. pointed out an enriched

Peer review under responsibility of Cairo University.
* Corresponding author.
E-mail address: moresr@usi.ch (R. Morese).

https://doi.org/10.1016/j.jare.2017.09.004
2090-1232/

bottom-up ventral-striatal dopamine release to incentive cues, gambling tasks and reward prediction, and possible inhibition of top-down orbito-frontal influences [5]. Indeed, dopamine agonist-related ventral-striatal hypo-functionality seems to be consistent with impaired risk evaluation [5]. An inability to resist an impropriate drive - usually of a hedonistic nature - and the consequent repetition of behaviors characterize ICD [6]. Pathological gambling; punding; hedonistic homeostatic behavioral disorder; hypersexuality; compulsive shopping; and binge eating are typical manifestations of ICD in PD [6,7]. The incidence of ICD in PD is as high as 40% of patients on dopamine agonist therapy and approximately 15% of patients overall [6]. An Italian non-interventional, prospective study on more than 1000 patients (ICARUS) has previously demonstrated that prevalence of ICD behaviors was relatively stable across the 2-year observational period (point prevalence: 28.6% at baseline, 29.3% at year 1, 26.5% at year 2) [7]. In this study, the most prevalent ICD subtypes were in line with literature. Moreover, authors have found that ICD-positive patients had more severe depression, poorer sleep quality and reduced quality of life [7]. Several risk factors are considered: younger age at onset, male sex, single status, a family/personal history of addictive behaviors, dopamine agonist medication in combination with levodopa treatment, high doses of dopaminergic medication, longer disease duration, long duration of pharmacological treatments, and a personality profile characterized by impulsiveness [6,7]. ICD appears to have some clinical overlap with compulsive behaviors (such as the compulsion for repetitive actions and the inability to inhibit intrusive thoughts) [8]. Moreover, ICD seems to share several features with drug addiction: (i) repetitive engagement in a behavior despite adverse consequences; (ii) diminished control over it; (iii) an appetitive urge/craving state prior to engagement; and (iv) a hedonic feeling experienced during the performance of the problematic behavior. All these features have led to a description of ICD as *behavioral addiction* [9]. The authors therefore hypothesized that this kind of "*impulsivity*" could be related with "*disinhibition of prepotent responses*".

The neuropsychological approach considers two measurable functions from which ICD can be detected: (i) integration of reward/punishment contingencies in individual choices, whose neural substrate is located in the orbito-prefrontal cortex; and (ii) response-inhibition, whose neural substrate is located in the inferior portion of the prefrontal cortex. impulsivity often develops from disturbed inhibitory control, a function mainly regulated by γ-Aminobutyric acid (GABA) levels in the anterior cingulate cortex (ACC) and the fronto-striatal system [10,11]. Interestingly, Li and colleagues identified the rostral cingulate as the area underlying poor performance in a response-inhibition task in cocaine-addicted subjects, with greater impulsivity correlating with ACC hypo-functionality [12]. Considering the above, the primary aims of this case report were: (i) to quantify psychometric (trait) and behavioral impulsivity in a PD patient with ICD; (ii) to evaluate the association between impulsivity and both response-inhibition and neural correlates of impulsivity measures. At the time of patient's examination, the authors hypothesized to obtain findings similar to the one proposed by Li et al. [10].

Case report

A 51-years-old man with a 12-year PD story, presenting motor fluctuations, and stable on 375 mg/day of levodopa was admitted to the hospital for the ascertainment of requirements for STN- deep brain stimulation (DBS) surgery. In 2014, the patient developed ICD symptomatology, including compulsive intake of sugary and high-fat food, and video-games dependence. Grazing behavior and hyper-focus on in-game achievements interfered with the patient's everyday life.

Neurological assessment was performed using the Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS). Motor features and disease severity were evaluated in On-/Off- conditions and scored using MDS-UPDRS part III and UPDRS total scores, respectively. Hoen and Yahr's (H-Y) was used to stage the disease. Neurological examination was negative except for bilateral bradykinesia and tremor of the upper limbs (MDS-UPDRS-III ON = 33; H-Y = 2).

The neuropsychological assessment was performed in the best-on phase, immediately after the neurological examination and the approval by the treating neurologist. The evaluation was based on the guidelines of the Task Force commissioned by the Movement Disorder Society to identify Mild Cognitive Impairment. These criteria provide an operational scheme based on two levels of assessment of the cognitive profile differing in their methods of evaluation and diagnostic certainty. Specifically, for the case described here, the first level of evaluation was applied. The assessment included the Mini-Mental State Examination (MMSE) and the Addenbrooke's Cognitive Examination – Revised version (ACE-R) to detect the presence of a general cognitive deterioration; attention, perceptual tracking of a sequence and speeded performance were analysed using the Attentional Matrices (AM) and Trail Making Test (TMT) part A; abstract reasoning and fluid intelligence using

Table 1
Neuropsychiatric and neuropsychological assessment in the on-phase of the disease. Where it is possible, maximum scores for each test are shown in square brackets. Wherever there is a normative value, the cut-off scores are given in the statistical normal direction; the values refer to the normative data for healthy controls matched according to age and education. Cells in grey indicate the absence of a normative cut-off.

Assessment		Scoring	Cut-off
Age (years)		51	
Education (years)		12	
Neuropsychiatric assessment			
AS	[42]	6	≤14
BDI	[39]	5	≤10
BAI	[63]	32	≤21
YMRS	[44]	1	≤12
BPRS 4.0	[168]	31	
HHD	[5]	2	
Neuropsychological assessment			
MMSE	[30]	30	≥24
ACE-R	[100]	89	≥82
FAB	[18]	14	≥13.48
Clinical Dementia Rating Scale		0	
AM	[60]	49	≥31
TMT A	[500]	57	≤94
TMT B	[500]	110	≤283
TMT B-A		53	≤187
FAS		29	≥17.35
Digit Span Forward	[9]	4	≥3.75
Rey-15 instant word test	[75]	43	≥28.53
Rey-15 delayed word test	[15]	9	≥4.69
CPM-36	[36]	29	≥18.96
WCST%		77.08	≥37.1
WCST% errors		22.91	
WCST% perseverative errors		27.27	≤42.7
Response Inhibition Task GO			
% Target		99,479	
Reaction Time (ms)		280,842	
Response Inhibition Task NOGO			
% Target		0	
% Errors		100	

N = frequency; AS = Apathy Scale; BDI = Beck Depression Inventory; YMRS = Young Mania Rating Scale; BPRS 4.0 = Brief Psychiatric Rating Scale version 4.0; HHD = Hedonistic-homeostatic-dysregulation scale; MMSE = Mini-Mental state Examination; ACE-R = Addenbrooke's Cognitive Examination – Revised version, FAB = Frontal Assessment battery; AM = Attentional Matrices; TMT = Trail Making Test; FAS = Verbal Fluency; CPM-36 = Coloured progressive Matrices-36; WCST = Wisconsin Card Sorting Test; GAM = Global Awareness of Movement Disorders; DS-I = Dyskinesias Subtracted-Index.

the Coloured Progressive Matrices (CPM-36); executive functions using the Frontal Assessment Battery (FAB), TMT-B, and the Wisconsin Card Sorting test (WCST); short-term and working memory abilities using Rey-15 word test and Digit Span (backward and forward, respectively). Lastly, information retrieval was evaluated using the Phonemic Fluency Test – letters F, A, S (FAS). Neuropsychiatric assessment included the Hedonistic-Homeostatic-Dysregulation scale (HHD), the Beck Anxiety Inventory (BAI), the Beck Depression Inventory (BDI), the Apathy Scale (AS), the Young Mania Rating Scale (YMRS) and the Brief Psychiatric Rating Scale 4.0 (BPRS 4.0).

Although the patient exhibited a normal global cognitive profile, reaching normative scores on the screening tests, abnormalities were detected for the performance on conceptualizing and response-inhibition tasks included in the FAB (Table 1). The neuropsychiatric assessment revealed significant levels of anxiety.

Neuroimaging data acquisition was performed on a 3T Philips Ingenia® scanner. Structural images of the whole brain were acquired using a T1-weighted sequence (TR = 4.8 ms, TI = 1650 ms, TE = 331 ms, voxel-size = $1 \times 1 \times 1$ mm^3). The MRI showed no alterations in the brain parenchyma signal (Fig. 1). During acquisition, the subject was asked to perform a response-inhibition paradigm (go/nogo task) in which the subject had to respond to go stimuli inhibiting the response to infrequent nogo stimuli (the letter "X" with a frequency of 17%) [4,5]. Functional data were acquired using T2*-weighted echo plannar image (EPI) (TR = 2.20 s, TE = 35 ms, slice-matrix = 64×64, slice gap = 0.28 mm, FOV = 24 cm, flip angle = 90°, slices aligned on the anterior commissure -posterior commissure [AC-PC] line). After scanning, the patient was asked to provide an estimate on the number of errors made in the experimental session. Considering the analyses, the authors selected a volume of interest encompassing the midcingulate zone, which has been shown to be specifically activated during tasks that require response selection and willful generation of motor behavior. This subregion of the ACC is located posterior to the genu of the ACC, anterior to the vertical plane passing through the anterior commissure [13,14].

In line with the authors' hypothesis on the role of response-inhibition disabilities and ACC hypofunctionality in the arising of impulsivity in this PD subject (see the introduction section), the patient completely failed the nogo task. He also showed difficulties in action-monitoring (in terms of number of detected nogo errors). In particular, despite errors in the nogo condition have reached 100% [40/40], the number of reported errors was 0. Moreover, the fMRI acquisition revealed unexpectedly total absent task-sensitive activity in the ACC and medial prefrontal cortex (MPFC) for the contrast nogo versus go (Fig. 1).

Discussion

The primary aim of the current work was to analyze the link between ICD, reduce response-inhibition and brain dysfunction in a 51-year-old man with PD that was admitted to the hospital for the ascertainment of requirements for STN-DBS surgery. This type of investigation could be very useful, since STN has been associated with neuropsychiatric changes, including ICD [3]. Indeed, the STN acts as a relay station for processing associative and limbic information before they are retransmitted to other brain regions, thus influencing behavioral changes [3]. In the limbic system, the amygdala acts as the integrative center for emotions, emotional behavior, and motivation [15]. Although amygdala is hypofunctioning in PD, dopamine replacement treatment induces amygdala hyperactivity [16]. Its dysfunction contributes to metacognitive-executive impairment, while ICD, hallucinations, anxiety, and panic attacks may appear in predisposed individuals [16]. Once considered these elements, it was decided to submit the patient to an overall cognitive test battery and behavioral assessment of mood changes.

Integration of reward/punishment contingencies in individual choices have been related with ICD. Significant activations during punishment behavior have been previously found in ventral tegmental area, right and left anterior insula, ACC, and the ventromedial prefrontal cortex [17]. ICD can also be detected by response-inhibition, which neural substrate is linked with ACC. In line with the neurocognitive approach, cingulate functionality was assessed with fMRI while the patient performed a go/nogo task that represents a classic paradigm in which the differing frequency of event types may result in response-related processing

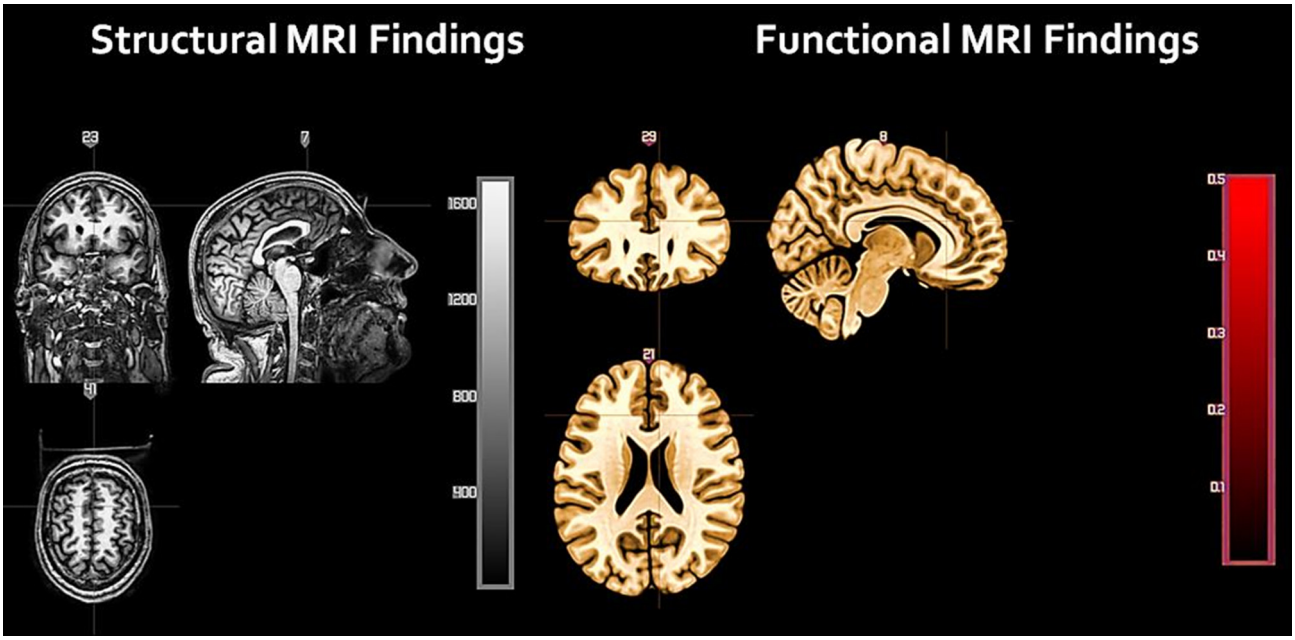

Fig. 1. Structural MRI image (T1-weighted sequence) and fMRI results for the contrast NOGO vs GO conditions were shown. Maps were thresholded at $p < 0.05$ cluster-level corrected using a small volume correction [SVC] with a sphere of 10 mm radius centered on ACC according to the coordinates reported in Palermo et al. [18] and Amanzio et al. [19].

conflict. The task involves visual discrimination and a simple choice: to respond (go) or not respond (nogo) depending on the current stimulus. Response conflict arises from competition between the execution and the inhibition of a single response (response-inhibition conflict), rather than from competition between two alternative responses (response-selection conflict). The experimental section revealed impairment of two basic executive functions: response-inhibition and action-monitoring (i.e., impaired error awareness) [13,14]. These alterations have been previously associated with a lack of recruitment of the medial prefrontal regions of the brain [13,14]. In particular, we have previously observed a relationship between action-monitoring and lower functionality in these brain regions in Bipolar Disorder patients unaware of their symptomatology when assessed with the same response-inhibition test [14]. These results are also in line with our previously published study on patients with AD and underline a reduced functional recruitment of the cingulo-frontal and parieto-temporal regions in patients with reduced awareness [13]. Action-monitoring disabilities could be explained by the nature of the executive deficits observed in this case report and involving fronto-striatal dysfunctions. Indeed, previous findings demonstrated that a specific executive dysfunction - related to action-monitoring, response-inhibition, and disinhibition - derives from ACC and MPFC hypo-functionality [13,14]. This finding has been found across pathologies and could have an underlying common etiopathogenetic mechanism.

Within this fronto-striatal circuitry, ACC and its connections could be considered part of an evaluative-affective network involved in behavioral inhibition [13]. Moreover, previous and current results consider the role of dopaminergic treatment on executive functions and metacognitive abilities in the medial prefrontal-ventral striatal non-depleted circuit [18,19]. Those results underline how the unawareness of distinct pathologies may exhibit overlapping symptoms in the context of overlapping circuit-specific dysfunction [14]. fMRI data advise that in this PD patient a functional alteration of the same cerebral network (involved in motor and behavioral disinhibition) could be possibly associated with ICD.

The evidences reported in this work suggest also that the execution of inappropriate motor responses reflects OFC, ACC, and MPFC hypo-functionality, and poor impulse control. Indeed, response-inhibition could be one of the motor/behavioral aspect of impulse control. Response-inhibition tasks may be useful in PD for better characterizing the clinical profile evaluating treatment options. It is relevant to note that ICD is a detrimental and underreported side effect of dopaminergic medication. Such an assessment is supposed to be particularly useful in the post-diagnostic phase, to better identify individuals at risk of developing ICD with dopaminergic medication.

Conclusions

ICD was associated with depressed mood, disinhibition, irritability, and appetite disturbance [20]. Moreover, many PD patients have difficulties with mental processing speed, response-inhibition, and shifting between different conceptual sets, suggesting frontal-executive dysfunction. The authors' hypothesis pointed out how "*behavioral addiction*" (i.e. "motor impulsivity") is related with "disinhibition of prepotent responses". Indeed, executive dysfunction in terms of response-inhibition could be a predisposing factor able to define the progression of ICD.

With this case report, a new suggestion for the comprehension of the neuropsychological and neural abnormalities involved in ICD was added. However, the relationship between ICD in Parkinson's disease and executive dysfunction is an intriguing question that has yet to be resolved. Future studies are needed to verify if the risk of ICD may best be determined through the integration of functional MRI and neuropsychological data involving response-inhibition measures.

Conflict of interest

The authors have declared no conflict of interest.

Compliance with Ethics Requirements

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from patient described in the report.

References

[1] Zgaljardic DJ, Borod DJ, Foldi NS, Mattis PJ, Gordon MF, Feigin A, et al. An examination of executive dysfunction associated with frontostriatal circuitry in Parkinson's disease. J Clin Exp Neuropsychol 2006;28:1127–44.
[2] Alexander GE, Delong MR, Strick PL. Parallel organisation of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 1986;9:357–81.
[3] Rossi PJ, Gunduz A, Okun MS. The subthalamic nucleus, limbic function, and impulse control. Neuropsychol Rev 2015;25:398–410.
[4] Ray N, Strafella AP. Dopamine, reward, and frontostriatal circuitry in impulse control disorders in Parkinson's disease: insights from functional imaging. Clin EEG Neurosci 2010;41:87–93.
[5] Voon V, Mehta AR, Harlett M. Impulse control disorders in Parkinson's disease: recent advances. Curr Opin Neurol 2011;24(4):324–30.
[6] Bugalho P, Oliveira-Maia AJ. Impulse control disorders in Parkinson disease: crossroads between neurology, psychiatry and neuroscience. Behav Neurol. 2013;547–557.
[7] Antonini A, Barone P, Bonuccelli U, Annoni K, Asgharnejad M, Stanzione P. ICARUS study: prevalence and clinical features of impulse control disorders in Parkinson's disease. J Neurol Neurosurg Psychiatry 2017;88(4):317–24.
[8] Ceravolo R, Frosini D, Rossi C, Bonuccelli U. Spectrum of addictions in Parkinson's disease: from dopamine dysregulation syndrome to impulse control disorders. J Neurol 2010;257(Suppl. 2):S276–83.
[9] Schreiber L, Odlaug BL, Grant JE. Impulse control disorders: updated review of clinical characteristics and pharmacological management. Front Psychiatry 2011;2:1.
[10] Courtney KE, Ghahremani DG, Ray LA. Fronto-striatal functional connectivity during response inhibition in alcohol dependence. Addict Biol 2013;18:593–604.
[11] Marsh R, Horga G, Parashar N, Wang Z, Peterson BS, Simpson HB. Altered activationin fronto-striatal circuits during sequential processing of conflict in unmedicated adults with obsessive-compulsive disorder. Biol Psychiat 2014;75:615–22.
[12] Li CR, Huang C, Yan P, Bhagwagar P, Milivojevic V, Sinha R. Neural correlates of impulse control during stop signal inhibition in cocaine dependent men. Neuropsychopharmacology 2008;33:1798–806.
[13] Amanzio M, Torta DM, Sacco K, Cauda F, D'Agata F, Duca S, et al. Unawareness of deficits in Alzheimer's disease: role of the cingulate cortex. Brain 2011;134:1061–76.
[14] Palermo S, Cauda F, Costa T, Duca S, Gallino G, Geminiani G, et al. Unawareness of bipolar disorder: the role of the cingulate cortex. Neurocase 2015;21:438–47.
[15] Janek HJ, Tye MT. From circuits to behavior in the amygdala. Nature 2015;517:284–92.
[16] Diederich NJ, Goldman JG, Stebbins GT, Goetz CG. Failing as doorman and disc jockey at the same time; amygdala dysfunction in parkinson's disease. Mov Disord 2016;31(1):11–22.
[17] Morese R, Rabellino D, Sambataro F, Perussia F, Valentini MC, Bara BG, et al. Group membership modulates the neural circuitry underlying third party punishment. PLoS One 2016;11(11):e0166357.
[18] Palermo S, Lopiano L, Zibetti M, Rosato R, Leotta D, Amanzio M. A novel framework for understanding reduced awareness of dyskinesias in Parkinson's Disease. Parkinsonism Relat Disord 2017;39:58–63.
[19] Amanzio M, Palermo S, Zibetti M, Leotta D, Rosato R, Geminiani G, et al. Self-unawareness of levodopa induced dyskinesias in patients with Parkinson's disease. Brain Cogn 2014;90:135–41.
[20] Pontone G, Williams JR, Bassett SS, Marsh L. Clinical features associated with impulse control disorders in Parkinson disease. Neurology 2006;67(7):1258–61.