Self-unawareness of levodopa induced dyskinesias in patients with Parkinson's disease.

Self-unawareness of levodopa induced dyskinesias in patients with Parkinson's disease

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Abstract

The study analyzes the presence of dyskinesias-reduced-self-awareness in forty-eight patients suffering from Parkinson's disease (PD). As the association with executive dysfunction is a matter of debate and we hypothesize it plays an important role in dyskinesias self-unawareness, we analyzed the role of dopaminergic treatment on the medial-prefrontal-ventral-striatal circuitry using a neurocognitive approach. Special attention was given to metacognitive abilities related to action-monitoring that represent a novel explanation of the phenomenon.

PD patients were assessed using different rating scales that we devised to measure movement awareness disorders. In order to ascertain whether each variable measured at a cognitive-clinical level contributes to predicting the scores of the movement-disorder-awareness-scales, we conducted multiple logistic regression models using the latter as binary dependent variables. We used the Wisconsin Card Sorting Test-metacognitive-version to assess the executive functions of the prefrontal-ventral-striatal circuitry.

Data showed that a reduction of self-awareness using the Dyskinesia rating scale was associated with global monitoring ($p = .04$), monitoring resolution ($p = .04$) and control sensitivity ($p = .04$). Patients failed to perceive their performance, distinguish between correct and incorrect sorts, be confident in their choice and consequently decide to gamble during the task.

We did not find any association with executive functions using the hypo-bradykinesia rating scale.

Our findings indicate that when the comparator mechanism for monitoring attentive performance is compromised at a prefrontal striatal level, patients lose the ability to recognize their motor disturbances that do not achieve conscious awareness.

Keywords

Awareness of movement disorders; Dyskinesias; Parkinson's disease ; Self-awareness ; Metacognitive functions.

1. Introduction

Levodopa-induced dyskinesias (LIDs) are one of the most common disabling motor complications in advanced Parkinson's disease (PD) (Fabbrini et al., 2007 and Jankovic, 2005). LIDs produce greater distress in caregivers (DeBettignies et al., 1990 and Seltzer et al., 1997) who judge patients more negatively than patients themselves (Marras & Lang, 2003). Indeed, patients who experience this symptom in the first person hardly ever complain about dyskinesias and simply tend to report a general worsening of the symptomatology. The subjective perception of motor impairment is an interesting phenomenon that has acquired a growing interest over the last few years.

Reduced awareness of neurological symptoms involves a wide domain of situations (Weinstein & Kahn, 1950). It is characterized by a failure to acknowledge a particular neuropsychological deficit relative to specific modular functions, in the specific case "action". As far as motor functions are concerned, anosognosia for Hemiplegia and anosognosia for dyskinetic movements were the most widely investigated symptoms. The proper term to define the relationship between anosognosia for dyskinetic movements and executive dysfunction (ED), in line with the most recent findings on patients with degenerative disorders and Acquired Brain Injury (ABI), is the term "reduced self-awareness" (Amanzio et al., 2011, O'Keeffe et al., 2007, Ownsworth et al., 2007, Ownsworth et al., 2008, Prigatano and Altman, 1990, Stuss and Anderson, 2004 and Stuss et al., 2001).

The hypothesis that dopaminergic overstimulation of mesocorticolimbic loops might be responsible for a reduction in the awareness of LIDs, in long term treated PD patients is currently accepted (Amanzio et al., 2010, Leritz et al., 2004, Maier et al., 2012 and Vitale et al., 2001). However, the relationship between unawareness of LIDs and ED in PD patients has not been solved yet. Indeed, the role of dopaminergic treatment in the executive functions (EFs) is complex. The findings of a systematic review and meta-analysis on PD patients supported the view that EF-impairments are evident even at the beginning of the disease (Kudlicka, Clare, & Hindle, 2011). However, the exact pattern of executive impairment remains unclear and the clinical significance has yet to be clarified (Kudlicka et al., 2011). Interestingly, the results showed that patients performed poorly in cognitive flexibility and, more specifically, in set switching and inhibition tasks. Only the performance of these particular tasks was impaired, but the whole spectrum of executive abilities was not compromised (Goldman et al., 2013).

The results obtained by the authors (Kudlicka et al., 2011) should be explained taking into account the different effects of dopaminergic stimulation on cognitive functions at the dorsolateral prefrontal level, on one hand, and on the medial prefrontal-ventral striatal circuitry (orbitofrontal and cingulated frontal-subcortical loops), on the other hand. In particular, it has been demonstrated that dopaminergic stimulation improves EFs related to the cortical-subcortical network, from the dorsolateral prefrontal cortex (DLPFC) to the dorsal caudate nucleus, which is dopamine depleted. On the contrary, the same dopaminergic treatment impairs functions connected to the medial prefrontal-ventral striatal non-depleted circuit (Cools, Barker, Sahakian, & Robbins, 2001), such as on tasks of attentional set-shifting and response inhibition (Dirnberger and Jahanshahi, 2013, Dujardin et al., 2001, Lewis et al., 2012, Muslimovic et al., 2005 and Werheid et al., 2007). In line with this, one of the most reliable mechanisms associated impaired self-awareness of LIDs with the deficits in executive functioning due to dopaminergic overstimulation of mesocorticolimbic circuits (Amanzio et al., 2010), while others have not found such a relationship (Jenkinson et al., 2009, Maier et al., 2012 and Pietracupa et al., 2013). It is noteworthy to emphasize how studies which have not found an association yet, have not used specific tests to assess EFs related to the medial prefrontal-ventral striatal circuitry. In particular, Maier et al. (2012) studied EFs through verbal fluencies, whereas Pietracupa et al. (2013) used phonemic and semantic fluencies, FAB and TMT. These

tests actually assess EF processes, particularly those related to the DLPFC. Precisely, the DLPFC is the primary neural substrate for most of the EFs such as: planning, strategic behavior, abstraction, working memory and attentional control (Leh, Petrides, & Strafella, 2010). Moreover, in the study by Jenkinson et al. (2009), despite the fact that the comparison was carried out between only 5 unaware and 10 aware patients, they had not found a relationship between unawareness of LIDs and the performance on the Brixton test, that assesses response inhibition abilities. Interestingly, the authors interpreted their results as a role of "action monitoring" in the reduction of LIDs awareness in terms of a breakdown in the error-detection process of intended and actual movement (Jenkinson et al., 2009) based on a well-established "forward" model of the motor system (Blakemore et al., 2001 and Wolpert, 1997). This hypothesis links LIDs unawareness and metacognitive functions, as others had suggested (McGlynn & Schacter, 1989).

We have recently demonstrated how a reduction in self-awareness is related to deficits in metacognitive functions i.e., the ability to inhibit a response, set-shifting and self-monitoring (Amanzio et al., 2013) and how unaware patients showed greater Anterior Cingulate Cortex (ACC) dysfunction (Amanzio et al., 2011, Palermo et al., 2014 and Palermo et al., 2014). As regards the influence of cognitive status on the awareness phenomenon, ACC had a crucial role in the control of action, such as attention-for-action-/target selection, motor response selection inhibition and error detection in performance monitoring. As impaired self-awareness is reported following PD (Amanzio et al., 2010), ABI (Palermo, Leotta, et al., 2014), frontotemporal dementia and Alzheimer's diseases (Amanzio et al., 2011, Amanzio et al., 2013 and O'Keeffe et al., 2007), we can hypothesize that these distinct pathologies exhibit metacognitive dysfunction in the context of overlapping circuits (Palermo, Leotta, et al., 2014).

The relationship we found between poor performance on the WCST and a reduction in the awareness of LIDs in PD patients (Amanzio et al., 2010) appears to be in line with a reduced functionality in ACC and, in more general terms, in the medial prefrontal-ventral striatal non-depleted circuit, during dopaminergic stimulation. As far as the link between the performance on WCST and ACC functionality it concerns, a PET study on healthy subjects showed that errors in the WCST correlated with dopaminergic D2/D3 binding in the right ACC (Lumme, Aalto, Ilonen, Någren, & Hietala, 2007). Another study has also clarified a role of the ventrolateral prefrontal cortex (BA 47/12) and ACC (BA 32) in performing the WCST in terms of increased activity during the reception of negative feedback (Monchi, Petrides, Petre, Worsley, & Dagher, 2001).

The main objective of the current study is to clarify the role of EFs primarily connected to the medial prefrontal-ventral striatal circuitry and the reduced sense of self-awareness of LIDs in cognitively preserved PD subjects. Importantly, our study is the first attempt to demonstrate the hypothesis that long-term dopaminergic treatment, can lead to mesocorticolimbic dopaminergic depletion involving the ventral striatum, might cause self-awareness of LIDs. We hypothesize that self-awareness of LIDs arises from disrupted EFs or metacognitive abilities, such as the new ones measured for the very first time in patients with PD using the metacognitive version of the WCST (Koren, Seidman, Goldsmith, & Harvey, 2006). In particular, we hypothesize action monitoring plays a special role, whereas other cognitive functions are preserved.

Finally, we considered a comparison between PD patients' predominantly left versus predominantly right-side motor symptoms at onset of disease, to assess the role of this phenomenon in the awareness of LIDs.

2. Materials and methods

2.1. Participants

Forty-eight patients (22 women, 26 men) with idiopathic PD receiving levodopa treatment, and presenting motor fluctuations were enrolled (Hughes, Daniel, Kilford, & Lees, 1992). Consecutive out-patients were recruited at the Neurology Division of the Department of Neuroscience and the Martini Hospital, both in Turin (Italy). Drug treatment has been carried out for about 9 years, whereas the appearance of dyskinesias occurred about 3 and a half years prior to the experimental evaluation. The pharmacological treatment was associated with dopamine agonists in 38 cases out of 48. The demographic and clinical data related to the PD patient population have been summarized in Table 1 and Table 2. The neuropsychological profile and detailed information relative to pharmacological treatment have been added for each patient in detail in the supplementary material.

Table 1
Clinical characteristics of the entire sample concerning the neurological and functional assessment of Parkinson's disease.

	Neurological assessment (mean ± SD)	On-phase (mean ± SD)	Off-phase (mean ± SD)
Age	65.79 ± 6.52		
Education (years)	9.08 ± 4.84		
Gender	26/22 (male/female)		
Years since the first symptoms appeared	11.48 ± 6.52		
Years since the diagnosis was made	10.40 ± 4.251		
Years after the beginning of L-dopa treatment	8.98 ± 4.15		
L-dopa (mg)	661.36 ± 286.78		
Years since the dyskinesia appeared	3.54 ± 2.97		
Hours of daily off	2.68 ± 2.35		
Hours of daily on	9.48 ± 4.40		
Hours of daily half-clutch	3.68 ± 4.03		
MDS-UPDRS total score		48.90 ± 21.06	73.10 ± 25.95
Part I		8.38 ± 7.36	8.96 ± 7.58
Part II		11.15 ± 5.91	16.35 ± 6.52
Part III		20.57 ± 12.59	39.82 ± 16.75
Part IV		8.08 ± 4.13	7.48 ± 3.22
Hoehn and Yahr scale		2.135 ± 0.75	2.57 ± 0.68

Mg = milligrams; SD = Standard Deviation.

Table 2

Demographic, neuropsychiatric and neuropsychological measures. Maximum scores for each test are shown in square brackets. As to BPRS, YMRS, BAI and BDI, higher scores indicate more severe symptoms. 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 gray indicate the absence of a normative cut-off.

	Neuropsychological assessment	Mean ± Std. Deviation	Cut -off
Off-Phase	AS [42]	11.38 ± 6.680	≤ 14
	BDI [39]	8.86 ±4.387	≤ 10
	BAI [63]	13.96 ±6.769	≤ 21
	YMRS [44]	2.83 ±3.428	≤ 12
	BPRS 4.0 [168]	37.41 ±8.371	
On-Phase	AS [42]	8.58 ± 5.62	≤ 14
	BDI [39]	8.29 ±4.69	≤ 10
	BAI [63]	13.63 ± 7.23	≤ 21
	YMRS [44]	3.15 ±4.12	≤ 12
	BPRS 4.0 [168]	38.58 ±8.41	
	HHD [5]	.85 ±.80	
	MMSE [30]	27.65 ±2.08	≥ 24
	TMT A [500]	80.08 ± 75.75	≤ 94
	TMT B [500]	253.10 ±166.12	≤ 283
	TMT B-A	180.25 ±138.10	≤ 187
	Fonemic Fluency	27.90 ±12.89	≥ 17.35
	Wechsler Memory Scale 4	7.191 ±4.16	
	Wechsler Memory Scale 7	13.777 ±4.55	
	ToM 1 [4]	3,85. ± .36	≥ 3
	Memory [4]	3.63 ± .49	
	Comprehension [4]	4 ± 0	
	ToM 2 [4]	3.56 ± .50	≥ 3
	Memory [4]	3.35 ± . 48	
	Comprehension [4]	4 ±0	
	WCST %	48.5558 ±15.71770	≥ 37.1
	WCST % errors	50.7698 ±17.29792	
	WCST % perseverative errors	35.9919 ±14.13202	≤ 42.7

AS = Apathy Scale; BDI = Beck Depression Inventory; BAI = Beck Anxiety 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; TMT = Trail Making Test; ToM = Theory of Mind; WCST = Wisconsin Card Sorting Test.

The inclusion criteria was a good clinical response to levodopa with the presence of wearing off or on–off phenomena and peak-of-dose dyskinesias. Patients were excluded from the study if they (a) had a random on–off; (b) early-morning and painful dystonia; (c) major depression or dysthymia, based on DSM-IV-TR criteria, (d) a Mini Mental State Examination score < 24 (MMSE) (Folstein, Folstein, & McHugh, 1975), (e) a history of neurological and psychiatric disorders (other than PD), such as hedonistic-homeostatic-dysregulation (HHD) (Giovannoni, O'Sullivan, Turner, Manson, & Lees, 2000), (f) were taking medications

that could directly impact cognitive functioning, other than dopaminergic therapy; (g) had undergone previous neurosurgery procedures including brain stimulation and/or pallidotomy/thalamotomy.
Patients participated in the study willingly and all gave their informed consent. The Ethics Committee approved this study.

2.2. Awareness of movement disorders and motor assessment

PD patients were compared on three different scales to measure awareness of movement disorders: (1) Global Awareness of Movement disorders (GAM: Amanzio et al., 2010), (2) Dyskinesia rating scale (DS: Amanzio et al., 2010) and (3) Hypo-bradykinesia rating Scale (HS: Amanzio et al., 2010). GAM is a 4-points semi-structured interview (0–3), where a high score corresponded to a high level of unawareness of movement disorders in relation to symptoms of dyskinesias. Scores were assigned by an experienced neurologist specialized in movement disorders according to the level of spontaneity with which the patients described dyskinesias in the on state versus hypokinesias/-bradykinesias in the off state. Dyskinesia and hypo-bradykinesia were separately evaluated by patients and the examiner to determine the effects of ongoing motor disturbances when the three simple motor tests were performed: (1) write a brief sentence; (2) lift a glass to your mouth; (3) stand up and walk around for five meters and sit down again. Scores range from 0 (absence of dyskinesia/hypo-bradykinesia) to 3 (severe and/or disabling dyskinesia/hypo-bradykinesia). Two different variables were obtained by subtracting the patient's score from that of the examiner: the Dyskinesias Subtracted-Index (DS-I) and the Hypo-bradykinesias Subtracted-Index (HS-I) (Amanzio et al., 2010). Higher scores were in line with a more severe reduction in awareness of movement disorders. As patient's own judgments, scores obtained on DS and HS should be defined in relation to patients' monitoring their own motor performance while performing action tasks.
In order to determine the role of side of onset on awareness of LIDs, a comparison was made between predominantly left-sided PD patients' versus predominantly right-sided patients when the disease began. Motor screening was performed using the revised Italian version of the Unified Parkinson Disease Rating Scale (MDS-UPDRS: Antonini et al., 2013), which was administered by neurologists who were blind to the purpose of the study. In particular, motor impairment was assessed on the basis of Section III. Disease stage was rated on the Modified Hoehn and Yahr Scale (Goetz et al., 2004).

2.3. Neuropsychological assessment

The overall assessment was based on the "Italian Health System – National Guideline System" for Parkinson disease (2013). It derives from the guidelines of the Task Force commissioned by the Movement Disorders Society to identify Mild Cognitive Decline (MCD-PD) (Litvan et al., 2012). These criteria provide an operational system-based on the two assessment levels of the cognitive profile that have different evaluation methods and diagnostic certainty.
Neuropsychological assessment included MMSE (Folstein et al., 1975) to detect the presence of a general cognitive deterioration; attention was analyzed using the Trail Making Test part A (TMT-A) (Spinnler & Tognoni, 1987); EFs using the TMT B and TMT B-A (Spinnler & Tognoni, 1987) and the Phonemic Fluency Test (Spinnler & Tognoni, 1987); memory abilities with the subscales IV and VII of the Wechsler Memory Scale (WMS) (Wechsler, 1945). Lastly, perspective-taking abilities were tested using Theory of Mind visual stories (ToM1 and ToM2) (Amanzio, Geminiani, Leotta, & Cappa, 2008).

With reference to EF assessment, it is important to underline that we evaluated EFs related to the DLPFC as mentioned above, and we also analyzed metacognitive-EFs which are primarily associated with the ventral striatal medial prefrontal circuit. In the current study, metacognition was evaluated using the metacognitive version of the WCST (Koren et al., 2006). The difference compared to the standard version we previously used (Amanzio et al., 2010) is represented by two requests: (1) the level of confidence expected from the response; (2) whether to include the response or not in the final score test. Each correct response implied a monetary bonus, or an incorrect response implied an equivalent penalty. The answer that was not included neither benefited nor harmed the penalty. In this way, both the forced response and the free choice response was achieved. Different metacognitive indexes were also obtained (Koren et al., 2006): (1) accuracy score (AS), the number of correct voluntary answers/number of voluntary responses; (2) free-choice improvement (FCI), (accuracy – number of correct responses from forced responses)/number of cards presented; (3) global monitoring (GM), the number of correct responses – the total number of sorts required in the final score; (4) monitoring resolution (MR), the gamma correlation calculated between the confidence and correctness of the sorts in the entire test; (5) control sensitivity (CS), to what extent the control process depended on the monitoring process, indexed by the gamma correlation calculated across all sorts between the level of confidence and the decision to gamble; (6) monetary gains (MG), given by the number of correct voluntary responses – incorrect number of voluntary responses.

Neuropsychiatric assessment included the Beck Depression Inventory (BDI) (Beck & Steer, 1987) and the Beck Anxiety Inventory (BAI) (Beck & Steer, 1993), the Apathy Scale (AS) (Starkstein et al., 1992), the Young Mania Rating Scale (YMRS) (Young, Biggs, Ziegler, & Meyer, 1978) and the Brief Psychiatric Rating Scale 4.0 (BPRS) (Morosini et al., 1994 and Roncone et al., 1999). Importantly, the psychiatric assessment of patients was not only performed in the on-phase but also in the off-phase in order to check and exclude a possible bias in the results.

2.4. Procedures

Patients were evaluated in the morning before drug therapy took place (off-state) and during the maximum-benefit-peak of the first daily dosage (on-state). As to the off-state, patients were assessed at least 12 h after therapeutic withdrawal, whereas they were assessed 90–120 min after treatment in the on state.

The neuropsychological assessment was performed during the on-phase for a period of about 2 h. The entire evaluation period lasted roughly 4 h.

2.5. Statistical analysis

Three separate multiple logistic regression models were used in order to estimate the impact of metacognitive disabilities in terms of WCST-metacognitive-version sub-items on GAM (0 = absent or slightly, 1 = moderate or severe), DS-I (0 = absent or slightly, 1 = moderate or severe) and HS-I (0 = absent or slightly, 1 = moderate or severe) outcomes respectively.

All estimates were adjusted for potential confounders such as: age, gender, duration of illness, L-dopa dosage and side of onset. Results have been presented as Odds Ratio (OR).

3. Results

The experimental sample consisted of 26 men and 22 women who had been diagnosed approximately 10 years before the experimental evaluation took place (see Table 1). The mean age of the samples was 65.79 years. The neuropsychiatric evaluation showed normative values in both of the evaluation phases: on and off (see Table 2). Furthermore, the neuropsychological assessment performed in the on-phase reported normal cognitive profiles (see Table 2).

We made a comparison between PD patients with predominantly left sided versus predominantly right-sided motor symptoms at onset of disease, to assess the role of this phenomenon in the awareness of LIDs. We did not find any relationship between the side of onset, the insurgencies of LIDs ($r = -.008$, $p = .961$), with the HS-I ($r = -.205$, $p = .157$) and the DS-I ($r = .247$, $p = .086$).

3.1. Awareness of movement disorders and metacognitive variables

After adjusting age, gender, duration of illness, L-dopa dosage and side of onset, the metacognitive variables assessed using WCST-metacognitive-version did not alter the probability that there may be a reduction of self-awareness using GAM or HS-I index. In other words, the probability of a reduction in self-awareness using GAM or HS-I were not influenced by: age, gender, duration of illness, L-dopa dosage and side of onset.

On the other contrary, the specific aspects of metacognition influenced the DS-I self-awareness outcome, such as higher control sensitivity that increased significantly the probability of DS-I (OR = 4.084, p = .047), and monitoring or global resolution that significantly reduced the probability of a moderate or severe DS-I score (OR = .022, p = .044; OR = .944, p = .055 respectively) (see Table 3).

Table 3

Results of the logistic regression analysis applied in order to estimate the effect of metacognitive aspects on the GAM, DS-I and HS-I scales. Outcomes were adjusted for potential confounders and are presented as Odds Ratio (OR). Bold Italics values showed that a reduction of self-awareness using the Dyskinesia rating scale was associated with control sensitivity, monitoring resolution and global monitoring.

		GAM		DS-I		HS-I	
Effect		OR	*p*	OR	*p*	OR	*p*
Monetary gains	MG	0.839	0.399	0.701	0.145	1.091	0.680
Control sensitivity	CS	0.745	0.606	***4.084***	***0.047***	0.58	0.340
Accuracy score	AS	1.034	0.944	0.411	0.115	0.82	0.640
Free-choice improvement	FCI	0.961	0.983	0.574	0.769	0.027	0.120
Monitoring resolution	MR	0.126	0.180	***0.022***	***0.044***	1.414	0.810
Global monitoring	GM	0.975	0.226	***0.944***	***0.055***	1.021	0.280

GAM = Global Awareness of Movement disorders scale; DS-I = Dyskinesia rating Scale Index; HS-I = Hypo-bradykinesia rating Scale Index.

4. Discussion and conclusion

The purpose of the current study is to analyze the link between reduced awareness of movement disorders and metacognitive-executive dysfunction from a neurocognitive perspective. We demonstrated in a previous study that PD patients showed a lack of awareness of movement disorders associated with executive functions and related to dyskinesias in the on state (Amanzio et al., 2010). Given the clinical significance of the results obtained, the current study evaluated 48 PD patients with the presence of wearing off or on–off phenomena and peak-of-dosage dyskinesias. Patients were studied on an overall neuropsychiatric-neuropsychological battery using specific tests to assess metacognitive executive functions. Our findings showed that a reduction of self-awareness using the Dyskinesia rating scale was associated with global monitoring, monitoring resolution and control sensitivity.

The inconsistency in the results previously obtained may have been due to a number of factors, presumably related to: the lower number of cases evaluated, the heterogeneity of the population including age of onset, severity and type of disease, the assessment of impaired awareness and, the most important aspect for our purpose, the complexity of the EF-construct itself. In particular, previous studies on LIDs awareness in PD have several limitations such, as the low number of patients evaluated (Jenkinson et al., 2009 and Vitale et al., 2001), the inclusion of patients with Mild Cognitive Impairment (Jenkinson et al., 2009 and Sitek et al., 2011) and, in some cases, cognitive deterioration was not excluded (Vitale et al., 2001). Moreover, patients were assessed using MMSE as a unique cognitive test (Leritz et al., 2004). A further critical aspect concerned the methods used to measure the presence of reduced awareness of LIDs in terms of patient–caregiver report discrepancies. In particular, in these cases it is crucial that any bias in caregivers' judgements is excluded (Amanzio et al., 2011, DeBettignies et al., 1990, Jorm, 1992, Jorm et al., 1994 and Ott and Fogel, 1992). Neuropsychiatric factors related to the disease were not properly assessed in a few studies. For example, only depression rating scales were administered (Kudlicka et al., 2011, Sitek et al., 2011 and Sitek et al., 2011) and no psychiatric assessment was performed (Jenkinson et al., 2009, Pietracupa et al., 2013 and Vitale et al., 2001). Importantly, an assessment on mood orientation should be considered carefully, as PD patients with depressed mood may perceive dyskinesias as a more significant problem, whereas patients with elevated mood may ignore the presence of dyskinesias as the drug has a rewarding effect (Sitek, Soltan, Wieczorek, Robowski, et al., 2011). Last of all, on considering the current study, the most critical aspect of the previous works on LIDs self-awareness in PD patients referred to a restricted assessment of executive functions (Jenkinson et al., 2009, Pietracupa et al., 2013 and Schacter, 1990) and did not evaluate the medial prefrontal-ventral striatal cognitive abilities. This last factor provides a possible reason for the lack of a relationship between reduced LIDs self-awareness and ED that do not take into account executive models of self-awareness. The latter should focus on the disruption of hypothetical higher order executive processes of self-monitoring and control (Amanzio et al., 2010, Amanzio et al., 2011, Amanzio et al., 2013, Palermo et al., 2014, Schacter, 1990 and Stuss and Levine, 2002).

In the current article we have confirmed the hypothesis that the disruption of prefrontal-subcortical connections may cause unawareness of LIDs associated with metacognitive dysfunction in non-deteriorated PD patients. In particular, we have strengthened our previous hypothesis (Amanzio et al., 2010) by directly assessing action monitoring using the metacognitive version of the WCST (Koren et al., 2006). We have used a neurocognitive perspective in order to illustrate the link between a reduction in LID-self-awareness, brain dysfunction and concomitant mild cognitive disturbances (Amanzio et al., 2011 and Palermo et al., 2014). The clinical group we evaluated was homogeneous in terms of disease duration and severity, pharmacological treatment and the cognitive and behavioral status was taken into consideration. The only

significant difference we observed, considering the WCST metacognitive version, was a reduction in LIDs self-awareness in patients with higher monitoring deficits. This result has strengthened our previous hypothesis as to a relationship between reduced awareness of hyperkinetic deficits, in the on-state, with the detrimental role of dopaminergic treatment on the prefrontal-subcortical loops producing specific metacognitive disabilities using regression analysis models. As patients were preserved considering the overall cognitive functions, the results that were obtained should be considered significant in order to interpret the self-awareness reduction of LIDs as specifically related to an impaired judgment capacity of metacognitive competence. In particular, the on-line emergent unawareness of deficits related to movement disorders in the on-state observed in our patients may be seen as an inability to monitor their dyskinesias. Interestingly, Flowers and Robertson (1985) stated that PD patients seemed less able to check their responses and inhibit errors during a cognitive task. This fact suggested they may be impaired in general response-monitoring. Recently, Jenkinson et al. (2009) hypothesized a role of "action monitoring" in the reduction of LIDs awareness in terms of a breakdown in the error-detection process of intended and actual movement. They linked LIDs unawareness and metacognitive functions, as others have already suggested (Leritz et al., 2004 and McGlynn and Schacter, 1989). As Jenkinson et al. (2009) hypothesized LIDs reduced awareness occurs due to a comparator failure and did not provide any association with EFs.

The conscious awareness model (CAM) (Agnew and Morris, 1998, Litvan et al., 1996, Litvan et al., 1997, Litvan et al., 2003 and Ryan et al., 2006) was developed to explain awareness deficits in AD and, may be fruitfully applied in both neurodegenerative disorders (O'Keeffe et al., 2007), in brain injury patients (Ownsworth et al., 2002, Prigatano, 1999 and Sherer et al., 1998) and currently in patients with PD, as we suggested previously (Amanzio et al., 2010). If the executive system is not functioning properly, the comparator mechanism may not pick up mismatches and therefore failures in motor performance may not achieve conscious awareness. Indeed, the results we obtained may be interpreted as patients' inability to self-monitor their motor performance with the impact of error considering tasks included in the Dyskinesias Rating Scale. In particular, patients with reduced LIDs awareness were less able in the confidence judgments, in the veridicality of one's overall sense of knowledge and in the decision to gamble on the entire task. Interestingly, only the DS-I was significantly related to monitoring, whereas the GAM based on the neurologist's judgment was not. A dopaminergic related mechanism of the results we obtained might be linked to error-related negativity. In particular, Stemmer, Segalowitz, Dywan, Panisset, and Melmed (2007), who used the event-related potential technique and an Eriksen flanker paradigm, found PD medicated patients had an attenuated error related negativity (NE/ERN) compared to those of healthy elderly controls at frontocentral scalp sites. The reduction in NE (generated in the ACC) was associated with poor performance monitoring (Holroyd & Coles, 2002).

The current study also analyzed the lateralization of hemispheric degeneration and the hypothesized link between severity of right basal ganglia degeneration and the presence of reduced awareness as suggested by others (Maier et al., 2012 and Pietracupa et al., 2013). The results we obtained are in line with our previous study and the hypothesis we addressed (Amanzio et al., 2010), where we did not observe a role for the lateralization of hemispheric degeneration in the presence of a reduced awareness, as others had found (Sitek, Soltan, Wieczorek, Robowski, et al., 2011).

In conclusion, the present study has also taken into account a measure of awareness of hypokinetic disorders, as we did in our previous work (Amanzio et al., 2010). In particular, we found patients only showed a selective reduction of awareness of movement disorders associated with metacognitive functions and related to dyskinesias in the on-state, compared to a preserved awareness of hypokinesias and no relationship with WCST metacognitive variables in the off-state. It is most important to understand this issue as poor LIDs self-awareness may bias clinical trials based on patients' motor diaries or may result in

prescribing increased dosages of dopaminergic drugs, which would in turn enhance the risk of side effects (Poletti & Bonuccelli, 2013).

Description of authors' roles

The study is based on a conception by Martina Amanzio who wrote the first draft of the study and participated in the review and critique processes. She also organized and designed the study and participated in the statistical analyses (review and critique). Sara Palermo performed the neuropsychological assessment (execution and organization) and also participated in writing the paper. Rosalba Rosato conducted the statistical analyses (execution). Maurizio Zibetti and Daniela Leotta performed the neurological assessment (execution and organization). Giuliano Geminiani supervised the assessment of unawareness of LIDs. Leonardo Lopiano supervised the neurological assessment, he took part in the organization of the study and participated in writing the paper (review and critique).

Acknowledgments

The study was approved by the Ethics Committee of the Martini Hospital in Turin (Italy). All subjects gave informed written consent to participate in the study.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at

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