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# Levodopa-Induced Dyskinesias and Dyskinesias-Reduced-Self-Awareness in Parkinson's Disease: A Neurocognitive Approach

*Sara Palermo, Rosalba Morese, Carlo Alberto Artusi, Mario Stanziano and Alberto Romagnolo*

## Abstract

Levodopa-induced dyskinesias are one of the most common disabling motor complications in advanced Parkinson's disease. The subjective perception of motor impairment is a clinical phenomenon that needs to be adequately analyzed. Indeed, the determination of patient dyskinesias-reduced-self-awareness (DRSA) and of its relationship to daily dysfunction is an important aspect of the debate on the gold standard for treatment. As the association with executive dysfunction is a matter of debate and we hypothesize it plays an important role in DRSA, we analyzed metacognitive abilities related to action monitoring and other factors, such as response-inhibition and "Theory of Mind," which represent a novel explanation of the phenomenon. Moreover, we investigated whether and how a dysfunction in action monitoring related to the cingulo-frontal-ventral striatal circuit would be associated with DRSA using an event-related Go-NoGo fMRI experiment. Our findings suggest the presence of executive dysfunctions in DRSA pathogenesis, with a key leading role played by the cingulo-frontal network as part of a functionally impaired response-inhibition network.

**Keywords:** dyskinesias, self-awareness, action monitoring, theory of mind, response-inhibition, fMRI, anterior cingulate cortex

## 1. Introduction

Parkinson's disease (PD) is a neurodegenerative disease with a slow but progressive evolution, which mainly involves the control of movements and balance. PD is part of a group of diseases called "movement disorders," and among these, it is the most frequent. The disease is present throughout the world and in all ethnic groups. It is found in both sexes, with a slight prevalence, perhaps, in males. The average age of onset is around 58–60 years, but about 5% of patients may present a juvenile onset between 21 and 40 years. Before the age of 20, it is extremely rare. Over the age of 60, it affects 1–2% of the population, while the percentage rises to 3–5% when the age is above 85.

The symptoms have perhaps been known for thousands of years: a first description would have been found in an Indian medicine treaty, which referred to a period of around 5000 BC. A more recent Chinese document dating back 2500 years is also known: “Huangdi Neijing” by Ti Huang [1]. However, the history of the disease is linked to the name of James Parkinson, a nineteenth-century London surgeon pharmacist, who first described most of the symptoms of the disease in a famous booklet, the “An Essay on the Shaking Palsy.”

PD is characterized by cardinal motor symptoms and several non-motor features. The former include bradykinesia, rigidity, and tremor, while the latter encompass autonomic symptoms, sleep disturbances, and neuropsychological disorders (i.e., cognitive impairment and dementia, affective disorders, impulse control disorder, psychosis) (see **Table 1**). In recent years, it has been understood that mild cognitive impairment associated with Parkinson's disease (PD-MCI) is more widespread than previously thought. It is estimated that 15–53% of total patients suffer from PD-MCI, with a higher frequency among the elderly and those with advanced Parkinson's disease. In 2012, the Movement Disorders Society commissioned a taskforce to unify the diagnostic criteria for PD-MCI. PD-MCI can be classified into *single-domain* and *multiple-domain* subtypes, each of which may show impairment in amnestic or non-amnestic domain [2]. Indeed, cognitive deficits associated with PD-MCI tend to involve frontal-based dysfunctions, including executive and attention/working memory deficits [3, 4]. Importantly, PD-MCI patients are at an increased risk of developing dementia (PDD), compared with cognitively intact PD subjects [5]. Neuropsychiatric symptoms such as apathy, visual hallucinations, and rapid eye movement sleep behavior disorders are often present. Attention processes, executive, recognition memory, and visuospatial dysfunctions tend to dominate [6]. In clinical practice, it is important that PDD should be recognized and appropriately treated [7].

After a first phase of the disease characterized by a good control of motor symptoms with the dopaminergic drugs (mainly levodopa and dopamine-agonists), patients inevitably enter the “advanced phase” of PD, developing the so-called motor complications, characterized by presence of involuntary movements (dyskinesia), painful dystonia, and re-emergence of parkinsonian symptoms (“off” periods) that can appear before the next levodopa dose (wearing-off) or suddenly (sudden or unpredictable “off”) (see **Table 1**). In the majority of cases, these complications occur alternately during the same day. Moreover, two opposite issues can

Cardinal motor symptoms	Motor complications	Involuntary movements	Non-motor complications
<ul style="list-style-type: none"> <li>• Bradykinesia</li> <li>• Rigidity</li> <li>• Tremor</li> </ul>	<ul style="list-style-type: none"> <li>• Motor fluctuations</li> <li>• Loss of answer to levodopa</li> <li>• Suboptimal response</li> <li>• End of dose deterioration</li> <li>• Wearing off</li> <li>• Awakening akinesia</li> <li>• On-off phenomena</li> <li>• Freezing</li> </ul>	<ul style="list-style-type: none"> <li>• Peak dose dyskinesia</li> <li>• Diphasic dyskinesia</li> <li>• “Off” state dystonia</li> <li>• “On” state dystonia</li> <li>• Yo-yoing</li> </ul>	<ul style="list-style-type: none"> <li>• Autonomic disorders (gastrointestinal, orthostatic hypotension, sweating, urologic, sexual dysfunction)</li> <li>• Sleep disorders (insomnia and sleep fragmentation, excessive daytime sleepiness, restless legs syndrome, rapid eye movement behavior disorder)</li> <li>• Sensory disorders</li> <li>• Mood disorders (depression, anxiety)</li> <li>• Psychosis</li> <li>• Cognitive impairment and dementia</li> </ul>

**Table 1.** Motor and non-motor complications and classification of levodopa-induced dyskinesias in advanced Parkinson's disease.

limit the adherence of patients to medical therapies in advanced PD phase. While for some patients, the need of dividing the levodopa daily dose in 5 or 6 administrations per day is considered a limitation, other patients develop a sort of craving for dopaminergic drugs, partly due to an impulse control disorder, and partly to a reduced awareness of therapy complications such as dyskinesia [8, 9].

The subjective experience of what it is like to be a PD patient is fundamental for the treatment complaint that is put at risk in cases of poor awareness of symptoms. Indeed, PD may result in reduced self-awareness of cognitive and behavioral symptoms. Moreover, patients may have reduced awareness of motor complications and—in particular—of dyskinesias secondary to the levodopa treatment. The determination of dyskinesias-reduced-self-awareness (DRSA)—and of its relationship to functional, behavioral, and neuropsychological (dys)functions—is a key aspect of the debate on the gold standard for treatment in PD. Considering the above, in this chapter, we will discuss therapies of the advanced phase and their management from a neurological and neuropsychological point of view; the case of levodopa-induced dyskinesias; the phenomenon of dyskinesias-reduced-self-awareness in PD; the neurocognitive approach to this phenomenon; the associated neuropsychological factor and neural underpinnings as well as from our research experience.

## **2. Parkinson's disease: therapies of the advanced phase and role of the neuropsychological evaluation**

Along with the progressive worsening of the disease and the motor complications, the patient's management could represent a difficult clinical challenge for physicians.

During the last two decades, the treatment of the PD advanced phase has radically changed with the advent of therapeutic options that include deep brain stimulation (DBS) of the subthalamic nucleus (STN) or globus pallidus internus (GPi), levodopa/carbidopa intestinal gel infusion (LCIG), and subcutaneous infusion of apomorphine [10]. These therapies demonstrated a significant and long-lasting improvement in the management of parkinsonian symptoms and motor complications but their application, in particular for DBS, needs a thorough evaluation of patients. In this scenario, the neuropsychological evaluation has acquired a leading role, due to the important implications of cognitive and affective status in the selection of the best advanced therapeutic option, and in the patient's follow-up. Both STN- and GPi-DBS proved to be effective in relieving PD cardinal symptoms and improving patients' quality of life. In fact, several studies demonstrated that DBS has a long-term efficacy in PD, yielding a 60% reduction on levodopa-related motor complications [11], a 40–60% improvement in quality of life [12], and a significant gain in quality-adjusted life years [13]. Since its breakthrough in 1987, about 150,000 patients worldwide were treated with DBS, which is now the most common and effective surgical procedure for advanced PD. However, the significant improvement obtained by patients is strictly related to the selection of the optimal candidates. Indeed, in 1999, the scientific community developed a “Core Assessment Program for Surgical Interventions in PD” (CAPSIT-PD) based on strict neuropsychological, clinical, and surgical inclusion criteria with the aim of improving the risk/benefit balance of PD patients undergoing neurosurgical procedures. According to the CAPSIT-PD criteria, it has been estimated that less than 10% of PD patients are suitable for DBS [14].

In general, the best PD surgical candidates have idiopathic Parkinson's disease (not parkinsonism); tend to be younger (below age 69, but may be older); have at least 30% improvement at the unified Parkinson's disease rating scale (UPDRS) part III after

levodopa administration; have medication-related complications, such as wearing-off of medications prior to the next dose, on-off fluctuations, and dyskinesias; and have no or mild cognitive dysfunction. The latter is one of the most controversial aspects of patient selection since many PD patients suffer from cognitive deficits also in the early phase of the disease, but are quite functional in their daily lives. Given the range of deleterious effects from PD-MCI/PDD and increased emphasis on neuropsychiatric features on patients' management, compliance to treatment and prognosis, there is a compelling need for a good neuropsychological evaluation. In particular, as part of the cognitive and mood preoperative assessment for DBS candidacy, the CAPSIT-PD committee recommended the following tests: Mattis Dementia Rating Scale (MDRS) and Montgomery and Asberg Depression Rating Scale for general screening and mood evaluation; verbal fluency (letters F, A, and S), Paced Auditory Serial Addition Test (PASAT), Odd Man Out (OMO), and Modified Brown Peterson Paradigm (MBPP) for the assessment of executive functions; Rey Auditory and Verbal Learning Test (RAVLT) and visual amnesic battery of Signoret for the assessment of explicit memory; and short version of Tower of Hanoi for the assessment of procedural memory.

Movement disorders centers that perform DBS have adapted the CAPSIT-PD protocol over time to fit the needs of their individual institutions, and in 2006, a report from the consensus on deep brain stimulation for Parkinson's disease, a project commissioned by the congress of neurological surgeons and the Movement Disorder Society, has been published to address all aspects of DBS preoperative decision-making [15].

Still, a high variability exists in the evaluation of good DBS candidates and the experience of the Movement Disorders Centers plays a major role in the patients' selection. Especially the cognitive assessment is relevant in the candidate selection, since dementia is the most frequent exclusion criterion for DBS surgery. This is due to three relevant aspects: (1) the vast majority of PD patients show some cognitive deficits, in particular, in the executive function domain; (2) dementia may be worsened by DBS; and (3) demented patients may not take advantage of the surgery-related improvement of motor symptoms. Given these premises, the clinical challenge is represented by the difficulty to know the extent of cognitive dysfunction that may affect the outcome of DBS. Moreover, while a thorough neuropsychological evaluation is mandatory within 1 year before DBS to exclude dementia, there is no consensus on the type of testing and level of performance that would exclude patients from receiving DBS. In 2007, the Movement Disorders Society established criteria for the diagnosis of PD dementia, and also proposed practical suggestions for their verification [16]. Nonetheless, it is common practice to repeat the evaluation after 6–12 months to ascertain that cognitive functions are stable when borderline cognitive deficits are outlined. Moreover, it is important to ascertain that cognitive dysfunction is not related to treatable causes such as depression or anti-parkinsonian medication, especially anticholinergics. Given an accurate candidate selection, DBS surgery showed excellent motor outcome with no or few neuropsychological issues. In fact, cognitive or affective symptoms may transiently appear as postoperative side effects but only rarely they are permanent. In particular, only the verbal fluency showed a significant deterioration after DBS and exclusively in STN-DBS-treated patients. Nonetheless, patients with preexisting mild cognitive impairment (MCI) have shown a shorter latency to dementia development in comparison with patients with presurgical normal cognitive status [17].

Finally, in patients treated with STN-DBS, particular attention needs to be paid for the affective state both in the selection phase and in the postsurgical follow-up, since depression and anxiety may worsen in some patients and few cases of suicides have been reported after surgery. Therefore, current psychiatric disorders and moderate to severe depression are further contraindication for DBS.

LCIG improves PD symptoms and motor complication [18] by means of a continuous delivery of levodopa directly in the jejunum, promoting stable plasmatic concentration and augmented bioavailability [19]. Unlike DBS, no strict neuropsychological indications are needed for starting LCIG treatment. Nevertheless, the patient's cognitive status has to be carefully evaluated. In fact, due to the gastrotomy and device management, the presence of severe cognitive impairment could unbalance the risk/benefit profile toward lower efficacy and higher prevalence of complications and side effects [20]. For the same reason, the presence of a caregiver is strongly recommended in patients with mild to moderate cognitive impairment undergoing LCIG treatment. On the other hand, LCIG does not seem to accelerate cognitive deterioration, and no significant differences in the long-term cognitive decline were reported in comparison with DBS or oral medical treatment [21]. Finally, amelioration of depression, anxiety, impulse control disorder, and psychosis has also been reported [20].

Subcutaneous infusion of apomorphine is a well-established treatment for advanced PD [22]. Similar to LCIG, no strict neuropsychological criteria exist for patient's selection, and no significant cognitive worsening seems to be associated with apomorphine infusion [23]. However, due to its powerful dopamine-agonist action, apomorphine treatment can be associated with acute confusional states, hallucinations, and paranoid psychosis. On the other hand, an improvement in mood and anxiety has been reported.

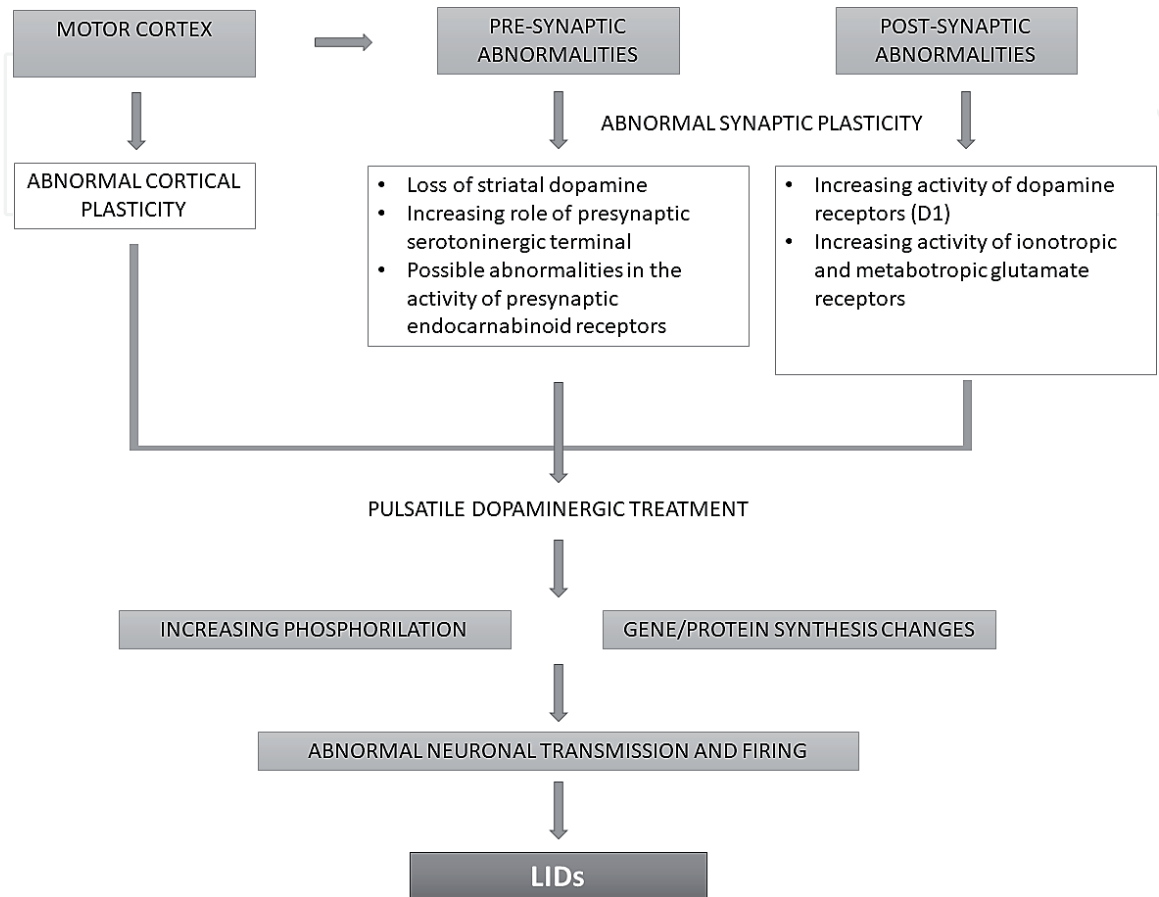
In conclusion, the management of the advanced phase of PD still represents a clinical challenge. A comprehensive neuropsychological evaluation is mandatory to guide the physician in the correct choice of treatment and to follow-up patients during the progression of the disease. The neuropsychological evaluation is also useful for understanding any dysfunctions in terms of "awareness of symptomatology" that may alter the compliance to the treatment and/or put the patient at risk in the daily living.

### **3. Levodopa-induced dyskinesias in Parkinson's disease**

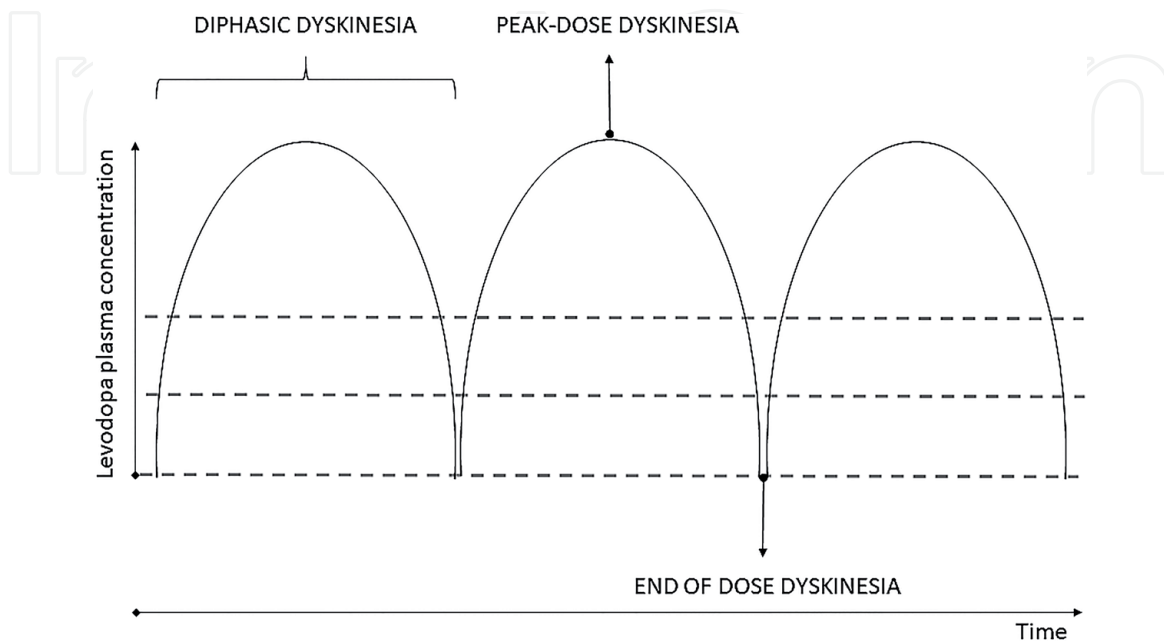
Levodopa is the most effective drug treatment for Parkinson's disease. However, its long-term use is complicated by disabling motor fluctuations and involuntary movements (the so-called levodopa-induced dyskinesias, LIDs) [24]. LIDs are involuntary choreiform ("soft") movements, which disturb the execution of voluntary movements and, when they are serious, cause very important disabilities in the patient. Dyskinesias are due to a denervation hypersensitivity of striatal neurons: changes in levodopa blood levels (dopamine precursor, with very short drug half-life) trigger dyskinesias because striatal cells—which have not received dopamine from the substantia nigra for long—become hypersensitive to the molecule. Despite significant advances, the pathogenesis of LIDs remains incompletely understood. It is known that dyskinesias appear only after dopaminergic therapy and there is a time lag between the start of treatment and the emergence of LIDs. Several possible mechanisms, both peripheral and central, have been proposed. A schematic representation of the whole process leading to LID is proposed in **Figure 1**.

LIDs are clinically heterogeneous [25]. LIDs generally first appear on the side worst affected by Parkinson's disease and in legs before arms [25]. Based on their relationship with levodopa dosing, LIDs are classified as peak-dose, end of dose, diphasic, off-state, on-state, and yo-yo dyskinesias (see **Table 1**). Peak-dose dyskinesias are the consequence of the maximum levodopa concentration (linked to an increase in dopamine at the synaptic level); diphasic dyskinesias are present both in growth and in decrease of the dopamine level; and end of dose dyskinesias are due

to a reduction of dopamine at the synaptic level. In this last case (or in the case of dystonia), we are in the presence of protracted movements that cause the patient to twist the neck, arms, legs, and hands (alterations of the harmonic regulation of the muscular tone between the agonist-antagonist muscle groups). They usually occur when the levodopa levels in the blood are low/reduced rapidly, more frequently at night or in the morning, before the first dose of levodopa (see **Figure 2**).



**Figure 1.** Schematization of the pathophysiological processes leading to the emergence of dyskinesias.



**Figure 2.** Main types of dyskinesias in relation to the plasma concentration of levodopa over time.

Once levodopa-induced dyskinesias have developed in patients, they are difficult to treat [24]. LIDs negatively affect patients' quality of life and substantially augment the costs associated with their health care [26]. Prevention of onset would therefore be the best strategy [25]. Recommended interventions include: controlled-release preparations of levodopa; continuous delivery of levodopa; using catechol-O-methyl transferase (COMT) inhibitors; using dopamine receptor agonists; and neuroprotective agents [25]. In the case of overt LIDs, some treatment options may include: reduction of levodopa doses; using dopamine receptor agonists; drugs acting on NMDA receptors; drugs acting on serotonergic systems; miscellaneous agents; and neurosurgery [25].

LIDs are certainly one of the most common disabling motor complications in advanced PD. Indeed, the subjective ability to perceive motor impairment is a clinical phenomenon that needs to be adequately analyzed. Reduced awareness of illness is one of the factors associated with medication nonadherence. Moreover, unaware parkinsonian patients are of particular concern to caregivers, as they may incur unnecessary risks in order to complete their daily activities, causing a deterioration of their own and others' quality of life [27].

#### **4. Dyskinesias-reduced-self-awareness (DRSA) in Parkinson's disease**

In clinical neuropsychology, "awareness of illness" is considered as a form of self-knowledge (the so-called "self-awareness"). Its construct is complex when considering an operational semantic level [28]. This term is used to describe the ability to identify, recognize, and evaluate a deficit in sensory, perceptual, motor, affective, or cognitive functioning and to consider the impact of these disturbances on the patient's daily life [8, 29–34].

Reduced self-awareness leads to numerous negative effects, such as augmented stress and burden for primary caregivers, families, personal care and health care partner. Moreover, it worsens patient-caregiver relations, eases deflection of mood, somatoform anxiety, and poor adherence to treatment [35]. Moreover, a reduction in self-awareness has been found to be associated with a decline in help-seeking behavior and compliance with medical treatment, presumably because of a reduction in motivation [34].

The neurocognitive approach considers cognitive functions and behavior as closely linked to the function of single brain area, neural pathways, or cortical networks. This approach emphasizes how reduced self-awareness is associated to brain pathology, particularly concerning focal lesions, motivational and emotional factors, and concomitant cognitive disturbances [8, 29–33, 36]. In particular, since the frontal lobes are involved in self-awareness and monitoring of cognitive functions, reduced self-awareness could be viewed as a deficit in self-monitoring [37]. Furthermore, deficits in the internal representation of external outputs have been suggested to be a possible mechanism of decreased awareness [32, 34, 38]. Indeed, any deficit in monitoring, response inhibition, or cognitive flexibility can affect patients' self-awareness [34, 35]. In our experience, patients with neurodegenerative disorders such as Alzheimer's and Parkinson's (PD) diseases or frontotemporal dementia show reduced self-awareness due to deficits in self-monitoring [8, 9, 29–31, 39, 49].

When considering PD, it may result in reduced self-awareness of cognitive and behavioral symptoms. A form of awareness reduction for dysexecutive [40–42] and mnemonic [43, 44] symptoms has been previously detected. If we consider the diagnostic spectrum ranging from complete cognition, to mild cognitive impairment (MCI), to the major neurocognitive disorder, a reduced self-awareness is



associated with the level of cognitive impairment and the simultaneous presence of mood abnormalities or executive dysfunctions [45]. In particular, reduced self-awareness has been detected in 36% of PD patients with mild dementia and 16% with MCI [45]. Moreover, more severe unawareness for cognitive impairment has been associated to depression, reduced hedonic tone, and more severe executive dysfunctions [45].

The phenomenon also manifests itself on the motor side. The determination of dyskinesias-reduced-self-awareness (DRSA)—and of its relationship to functional, behavioral, and neuropsychological (dys)functions—is a key aspect of the debate on the gold standard for treatment in PD. However, the relationship between subjective and objective evaluations of motor symptomatology in PD has so far been poorly investigated. Previous evidence has shown that parkinsonian patients have deficits in the subjective evaluation of levodopa-induced dyskinesias, with percentages ranging from 23 to 61% [39, 46–49]. Importantly, the hypothesis that dopaminergic overstimulation of mesocorticolimbic loops might be responsible for DRSA is currently suggested [8, 9, 39]; however, the role of dopaminergic treatment in the occurrence of metacognitive-executive dysfunctions is not yet fully clarified and requires more attention from the scientific community. Importantly, the kind of association between DRSA and executive dysfunction in PD patients has not been solved yet [8, 9, 49].

## **5. The proposal of a neurocognitive model of DRSA in Parkinson's disease**

Reduced self-awareness may be considered an organically based decreased/lack of insight about neurological, cognitive, and behavioral deficits [34]. After a brain damage, sometimes patients become unable to detect the presence—or to realistically assess the severity—of sensory deficits, and motor, affective, or cognitive impairments, although, they are evident to doctors and family [34].

“Self-awareness” is a complex neuropsychological notion, defined as “the ability to consciously process information about ourselves in a manner that reflects a relatively objective view while maintaining our unique phenomenological or subjective sense of self” ([50], p. 301). Indeed, self-awareness is above all a form of self-knowledge and a higher-order cognitive function covering information about the state of the disease, its functional consequences, the way in which it affects the patient and influences his/her interaction with the environment [34].

A neurocognitive model of awareness may help in understanding the contribution of metacognitive-executive abilities related to DRSA in PD [8, 9, 34, 49]. Indeed, it is possible to interpret a reduction in disease awareness by referring to the *Cognitive Awareness Model* (CAM), which incorporates a comparator system within the central executive to detect mismatches between a personal database and experience of failures and successes [51]. When a discrepancy is found, a signal is sent out to the metacognitive awareness system, enabling a conscious experience of failure/success. If the executive system does not work properly, the comparator mechanism may not detect mismatches, and subsequently experienced failures may not produce any metacognitive output or conscious awareness, leading to an “executive unawareness” in the CAM [51]. In line with the interpretative model associating DRSA with executive dysfunction [8, 9, 34, 49], if the comparator mechanism for “attentive performance-monitoring” is compromised, then PD patients lose the ability to recognize their motor disturbances and levodopa-induced dyskinesias do not achieve conscious awareness.

## **6. Neuropsychological factors associated with DRSA**

In their first study, Amanzio et al. [39] evaluated the presence of awareness of movement disorders in 25 PD patients. None before have analyzed the differences in DRSA by comparing the “on” and “off” states. PD patients were compared on three different scales to measure awareness of movement disorders: global awareness of movement (GAM) disorders, dyskinesia/hypo-bradykinesia rating scales. The authors found that PD patients had greater awareness and psychological suffering in the “off” than in the “on” state: patients explicitly complained about hypokinesias, mood-related symptoms, and perceived disability in their daily living [39]. Importantly, patients only showed DRSA in the “on” state and this reduced awareness was associated with executive cognitive dysfunction [39].

Since the dopaminergic overstimulation of mesocorticolimbic pathways may cause a dysfunction of prefrontal-subcortical connections and, subsequently, may negatively affect executive functions, more attention has been given to metacognitive-executive abilities related to action monitoring, that represent a novel explanation of DRSA [49]. The Wisconsin Card Sorting Test-metacognitive-version [52] turned out to be a fruitful neuropsychological tool to assess the executive functions of the prefrontal-ventral-striatal circuitry [49]. Indeed, DRSA was associated with global monitoring, monitoring resolution, and control sensitivity, suggesting that when the comparator mechanism for monitoring attentive performance is compromised at a prefrontal striatal level, patients lose the ability to recognize dyskinesias and to be aware of nonvoluntary movements [49]. These results support the interpretive efficacy of the CAM model not only in the case of major neurocognitive disorders [29–31], acquired brain injuries [33], and neuropsychiatric disorders [33], but also in the case of movement disorders.

Although dyskinesias-reduced-self-awareness in PD is related to deficit in metacognition, other factors, such as “Theory of Mind” (ToM), could operate [8]. Indeed, ToM has been a topic of interest in recent studies on unawareness of disease in neuropsychiatric disorders such as schizophrenia and bipolar disorder [33]. Not only decreased self-awareness may be considered a critical manifestation of impaired ToM abilities—in terms of meta-representation—but second-order false belief tasks and affective ToM abilities [33] seem to be of critical importance for preserved awareness of illness. For all the above, Palermo and collaborators [8] investigated whether DRSA could be influenced by cognitive and affective ToM as a contributing factor that has not yet been evaluated. Perspective-taking abilities were tested using ToM visual stories [53], while the ability to recognize the mental state of others was tested using the Reading the Mind in the Eyes task [54]. Multiple logistic regression models were used to estimate the impact of ToM disabilities on awareness evaluation [8]. DRSA was associated with the automatic and rapid processes of decoding mental states [8], which have often been ascribed to the affective ToM subcomponent [54]. Moreover, the association with executive dysfunctions has been reconfirmed [8].

## **7. New findings concerning the association between executive functions and the neural correlates of DRSA**

We have previously demonstrated a noteworthy association between DRSA and decreased functional recruitment of the cingulo-frontal and cingulo-opercular pathways due to prolonged iatrogenic overstimulation [8, 39, 49]. This kind of association engaged in loading executive-monitoring onto the processing of task-relevant information, so as to avoid interference by goal-irrelevant stimuli.

Importantly, response-inhibition dysfunction is often observed in PD. Besides being involved in response-inhibition tasks, the anterior cingulate cortex is part of a functional system based on self-awareness and engaged across cognitive, affective, and behavioral contexts [9]. Considering the above—and since a dysfunction in action monitoring related to the cingulo-frontal-ventral striatal circuit would be associated with DRSA—it is important to evaluate whether and how ACC could be involved in the arising of DRSA in PD.

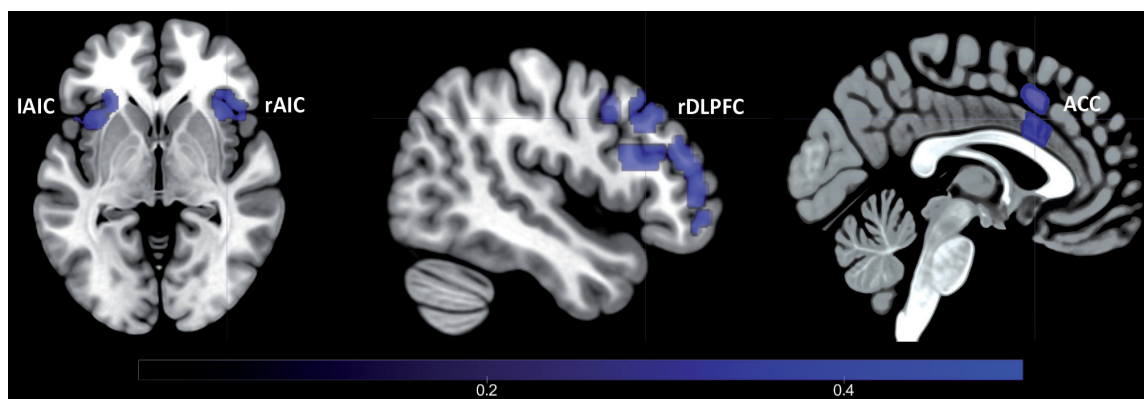
The association between blood oxygenation level-dependent response over the whole brain during an ACC-sensitive response-inhibition task and DRSA was investigated to clarify the kind of association between brain dysfunction and concomitant cognitive-behavioral disturbances [9]. The proposed paradigm is a prototypical task to measure the ability to inhibit an overpowering response [55, 56]. 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) [55, 56].

DRSA was associated with a reduced functional recruitment in the bilateral ACC, bilateral anterior insular cortex, and right dorsolateral prefrontal cortex ( $p < 0.05$ ) (see **Table 2** and **Figure 3**). Moreover, DS-I scores significantly correlated with percent errors on the NoGO condition ( $r = 0.491$ ,  $p = 0.009$ ). Indeed, the worse the response-inhibition's performance, the worse the ability of a subject to notice and adequately assess the severity of his/her own dyskinesias [9].

Brain areas	MNI coordinates			Voxels	r-Score	p-Value
	X	Y	Z			
ACC	4	26	29	982	-0.84	0.000
ACC	-5	25	27	798	-0.81	0.000
AIC	33	22	-4	1855	-0.64	0.001
AIC	-39	27	3	1654	-0.41	0.002
DLPFC	-45	10	47	2128	-0.39	0.007

Peak activity coordinates are given in MNI space. Peak activities are significant at  $p < 0.05$ , FWE corrected for multiple comparisons at the voxel level. ACC: anterior cingulate cortex; AIC: anterior insular cortex; DLPFC: dorsolateral prefrontal cortex.

**Table 2.** Linear correlation between the “NoGO” vs. “GO” contrast and DS-I scores (FWE  $p < 0.05$ ).



**Figure 3.** Brain area negatively associated with DRSA in the NoGO/GO contrast (adapted from [9]).

## 8. Conclusions

Our findings show how DRSA was related with metacognitive-executive functions and the affective component of ToM, thus caused by a complex interplay between specific neuropsychological and motor factors.

Executive functions are a predictor of DRSA pathogenesis, with a key role played by ACC. Imaging biomarkers for DRSA are important to be studied, especially when the neuropsychological assessment seems to be normal. Our findings suggest 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.

It is important to consider the specific neuropsychological characteristics (including DRSA and metacognitive-executive (dys)functions) along with the neurological symptoms to define tailored interventions and adopt a personalized clinical approach avoiding increased doses of dopaminergic drugs, which would in turn enhance the risk of side effects.

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## Conflict of interest

No conflicts of interest considering all the authors.

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