Parkinsonism and Related Disorders xxx (2017) 1–6

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

A novel framework for understanding reduced awareness of dyskinesias in Parkinson's Disease

Sara Palermo [a], Leonardo Lopiano [a, b], Maurizio Zibetti [a], Rosalba Rosato [c, d], Daniela Leotta [e], Martina Amanzio [b, c, *]

[a] Department of Neuroscience, Via Cherasco 15, 10126 Turin, Italy
[b] Centro Interdipartimentale di Studi Avanzati in Neuroscienze - National Institute of Turin (NIT), Regione Gonzole 10, 10043 Orbassano, Italy
[c] Department of Psychology, University of Turin, Via Verdi 10, 10123 Turin, Italy
[d] Cancer Epidemiology Unit, "Città della Salute e della Scienza" Hospital, Turin, Italy
[e] Martini Hospital, Via Tofane 71, 10141 Turin, Italy

ARTICLE INFO

Article history:
Received 19 October 2016
Received in revised form
6 March 2017
Accepted 13 March 2017

Keywords:
Parkinson's disease
Dyskinesias
Self-awareness
Theory of Mind
Reading the Mind in the Eyes

ABSTRACT

Background: Although dyskinesias-reduced-self-awareness (DRSA) in Parkinson's disease (PD) is related to deficit in metacognition, other factors, such as "Theory of Mind" (ToM), could operate.
Methods: Forty-one PD patients were assessed using the Global Awareness of Movement Disorders (GAM) and the Dyskinesias Subtracted-Index (DS-I). To study whether GAM and DS-I scores could be influenced by second-type ToM or Reading the Mind in the Eyes (RME) tasks, we conducted two multiple logistic regression analyses.
Results: The association between the GAM, the DS-I and RME task were highly significant. The association between DS-I and Trail Making Test B-A version was also verified.
Conclusion: DRSA was related with affective component of ToM and executive functions, thus caused by a complex interplay between specific neuropsychological and motor factors.

1. Introduction

Levodopa-induced dyskinesias are one of the most common motor complications in advanced Parkinson's disease (PD). PD is also characterized by a complex and variable spectrum of cognitive and behavioral symptoms; however, the subjective perception of motor impairment is a clinical phenomenon that needs to be adequately analyzed. Importantly, PD patients may be partially or even completely unaware of the presence of involuntary movements in terms of dyskinesias-reduced-self-awareness (DRSA). Unaware PD patients may engage in potentially dangerous activities, to compensate for their difficulties in performing activities of daily living or to comply with therapy [1]. This abnormal subjective perception of motor impairment is a clinical phenomenon that can provide suggestions about the progression of the disease, treatment adherence, the patient's quality of life and the associated distress of the caregiver [1].

DRSA is characterized by a failure to acknowledge a particular neuropsychological deficit relative to specific functions, in the case in question, "action" [2]. The phenomenon has attracted growing interest in recent years [1–5]. In previous studies, approximately half of PD patients were found to have DRSA to some extent [3–5]. In particular, our own studies [2,3] observed a reduction in the awareness of dyskinesias in 44% and 53% of patients, respectively. Moreover, in the study by Sitek et al., 43% of patients rated their dyskinesias as less severe than did their caregivers [6]. More recently, DRSA was reported in 61% and in 23% of patients [4,5].

Dopaminergic overstimulation of mesocorticolimbic circuitries might be responsible for DRSA [2–4]. Moreover, the association between DRSA and executive dysfunction due to this kind of overstimulation seems to be significant [2,3]. Although some authors have not found such an association [1,4,5], the limitations of these studies, which obtained negative results, have recently been reported [2].

In line with the interpretative model associating DRSA with executive dysfunction, if the comparator mechanism for "attentive-performance-monitoring" is compromised, then PD patients lose the ability to recognize their motor disturbances and levodopa-

* Corresponding author. Department of Psychology, University of Turin, Via Verdi 10, 10123 Turin, Italy.
E-mail address: martina.amanzio@unito.it (M. Amanzio).

http://dx.doi.org/10.1016/j.parkreldis.2017.03.009
1353-8020/

Abbreviation list

AS	Apathy Scale
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
BPRS 4.0	Brief Psychiatric Rating Scale version 4.0
DRSA	Dyskinesias-reduced-self-awareness
DS	Dyskinesia rating Scale
DS-I	Dyskinesias Subtracted - Index
FAS	Verbal Fluency – letters F, A, S
GAM	Global Awareness of Movement Disorders
HHD	Hedonistic-Homeostatic-Dysregulation scale
LID	Levodopa-Induced Dyskinesia
MDS-UPDRS	Movement Disorder Society - Unified Parkinson Disease Rating Scale
MMSE	Mini Mental State Examination
PD	Parkinson's Disease
RME	Reading the Mind in the Eyes Task
TMT	Trail Making Test
ToM	Theory of Mind
ToM 1	Theory of Mind – 1st order belief task
ToM 2	Theory of Mind – 2nd order belief task
YMRS	Young Mania Rating Scale
WCST	Wisconsin Card Sorting Test

induced dyskinesias do not achieve conscious awareness [1,7]. We have previously demonstrated the detrimental role of dopaminergic treatment on the prefrontal-subcortical loops producing DRSA linked to specific metacognitive disabilities in terms of global monitoring [2,3].

Based on our current knowledge, DRSA should not only be assessed in the light of an association with executive and metacognitive functions (i.e. monitoring abilities). There is another possible intervening factor that must be emphasized: the “ability to mentalize”, to understand the mental state of others and to predict behavior based on those states, also defined as “Theory of Mind” (ToM) [8].

Theory of Mind has been a topic of interest in recent studies on unawareness of disease in neuropsychiatric disorders such as schizophrenia [9,10]. Interestingly, a reduction in self-awareness may be considered a critical manifestation of impaired ToM abilities, in terms of meta-representation in this kind of disorder. This inference was confirmed by Bora and colleagues [9], who found that second-order false belief tasks seem to be of critical importance for awareness of the disorder [9]. Moreover, a study on the awareness of illness in bipolar disorder reported an association between a decreased awareness and a selective disability on affective ToM tasks [11].

Although ToM [12] and recognition of facial emotion [13] are impaired in PD patients, to the best of our knowledge no previous studies have investigated the ToM components in self-awareness of motor deficits in PD patients.

The aim of the current study is to investigate whether DRSA could be influenced by cognitive and affective ToM as a contributing factor that has not yet been evaluated. In particular, ToM tasks that explore both the cognitive and affective subcomponents were administered to 41 cognitively preserved patients in order to address the following questions: a) Might DRSA be related to ToM dysfunction? b) Which of the two ToM subcomponents is more involved in DRSA?

2. Material and methods

2.1. Participants

Forty-one patients (18 women, 23 men) with idiopathic PD receiving levodopa treatment, and presenting motor fluctuations were enrolled. Consecutive outpatients were recruited at the Neurology Division of the Department of Neuroscience and the Martini Hospital, both in Turin (Italy). The pharmacological treatment had been ongoing for about 9 years and consisted of levodopa associated with dopamine agonists in 28 cases out of 41. Dyskinesias appeared about 4 years before the neuropsychological evaluation. Tables 1 and 2 summarize the demographic and clinical data of the PD sample. For each patient, the neuropsychological profile and detailed information about the pharmacological treatment are reported in the supplementary online material (supplementary Tables I–IV).

A good clinical response to levodopa with the presence of wearing off or on-off phenomena and peak-of-dose dyskinesias was the first required selection criteria. Patients were only included in the study if they *(a)* did not have a random on-off; *(b)* did not have early-morning and painful dystonia; *(c)* did not show behavioral abnormalities such as major depression or dysthymia, based on DSM-V criteria, *(d)* did not have a history of neurological or psychiatric disorders (other than PD), such as hedonistic-homeostatic-dysregulation, *(e)* were not taking medications that could directly impact cognitive functioning, other than dopaminergic therapy; *(f)* had not undergone previous neurosurgery procedures including brain stimulation and/or pallidotomy/thalamotomy; *(g)* had a Mini Mental State Examination score $\geq$ 25 (MMSE), in order to include only cognitively non-impaired subjects.

2.2. Assessment of DRSA and neurological evaluation

PD patients were compared on two different scales to measure awareness of movement disorders: I) Global Awareness of Movement Disorders (GAM: [2,3]) and II) Dyskinesia rating Scale (DS: [2,3]).

I) The GAM is a 4-point semi-structured interview, where a high score corresponds to a severe level of DRSA. Scores were assigned by a neurologist experienced in movement disorders and based on the degree of spontaneity with which subjects reported dyskinesias in the on state.
II) The severity of dyskinesias was evaluated separately by the patient and the examiner. The patient was asked to write a short sentence and execute some verbal commands; scores were assigned from 0 (total absence of Dyskinesia) to 3 (severe Dyskinesia) on the DS in relation to the patient's performance. A dyskinesia index (DS-I) was calculated by subtracting the patient's judgments from those of the examiner on the DS. Higher scores indicated more severe DRSA and error detection in performance monitoring.

Motor screening was performed using the revised Italian version of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS: [14]), which was administered by neurologists blind to the aim of the study. In particular, motor impairment was assessed on the basis of Section III. Dyskinesias were assessed using Section IV: the rater uses historical and objective information to assess time spent with dyskinesias and their functional impact. Time spent *off*

Please cite this article in press as: S. Palermo, et al., A novel framework for understanding reduced awareness of dyskinesias in Parkinson's Disease, Parkinsonism and Related Disorders (2017), http://dx.doi.org/10.1016/j.parkreldis.2017.03.009