



Impaired awareness of movement disorders in Parkinson's disease

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ABSTRACT

Background: This study analyzed the presence of awareness of movement disorders (dyskinesias and hypokinesias) in 25 patients with Parkinson's disease (PD) and motor fluctuations (dyskinesias, wearing off, on–off fluctuations). Of the few studies that have dealt with this topic, none have analyzed the differences in the awareness of motor deficits by comparing the on and off states using motor scales and an extensive battery of tests to assess cognitive and behavioral functioning.

Methods: PD patients were compared on three different scales that we have devised to measure awareness of movement disorders: Global Awareness of Movement (GAM) Disorders, dyskinesia/hypo-bradykinesia rating scales.

Results: Data showed that PD patients had greater awareness and psychological suffering in the off state than in the on state. In particular, they were troubled by motor disabilities related to hypokinesias and had mood-related symptoms and a perception of disability in activities of daily living. Interestingly, patients only showed a selective reduction of awareness of movement disorders associated with executive functions and related to dyskinesias in the on state, compared to a preserved awareness of hypokinesias in the off state. On the contrary, no association with executive functions was found in the off state.

Conclusion: Our findings suggest that the dopaminergic overstimulation of mesocorticolimbic pathways may cause a dysfunction of prefrontal–subcortical connections related to the impaired insight.

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1. Introduction

Parkinson's disease (PD) is a progressive, neurodegenerative disorder, characterized by complex motor impairment with both hypokinetic (hypo-bradykinesia) and hyperkinetic (resting tremor) symptoms. The neuropathological hallmark of PD is the degeneration of dopaminergic neurons of the substantia nigra pars compacta (Jellinger, 1987), leading to dopaminergic denervation of the striatum, which is the first aspect to occur. Subsequently, as the disease progresses, other dopaminergic systems are involved; in particular, the mesocorticolimbic dopaminergic depletion diffuses to the ventral striatum (Agid et al., 1993; Kish, Shannak, & Hornykiewicz, 1988) producing mild executive function deficits and behavioral alterations (Owen et al., 1992; Taylor, Saint-Cyr, & Lang, 1986). The role of dopaminergic treatment on motor, behavioral and cognitive dysfunctions is complex. From a motor perspective, the efficacy of treatment with levodopa (precursor of

dopamine) is complicated by motor fluctuations with dyskinesias and wearing off or on–off states.

Although PD is characterized by a complex and changeable spectrum of symptoms, the subjective perception of motor impairment is an interesting phenomenon that has been inadequately analyzed. Reduced awareness of neurological symptoms, defined as "anosognosia", can involve a wide domain of situations (Weinstein & Kahn, 1950). In particular, in the domain of motor functions the most widely investigated symptoms are anosognosia for hemiplegia and anosognosia for dyskinetic movements (Myslobodsky, 1986; Shenker, Wylie, Fuchs, Manning, & Heilman, 2004). The phenomenon of anosognosia could be considered in terms of at least two different theoretical frames. For the motor-sensorial domains of anosognosia, such as hemiplegia, an impairment of a modular system of awareness can be hypothesized (Bisiach & Geminiani, 1991). On the other side, prefrontal–striatal dysfunction of the executive monitoring system could have a role in other domains of reduced awareness (McGlynn & Schacter, 1989). For example, it has been suggested that a dysfunction of the Central Executive System (Baddeley, 1986) may account for the lack of awareness in Alzheimer's disease (AD) patients (Amanzio & Torta, 2009;

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Lopez, Becker, Somsak, Dew, & DeKosky, 1994). This second type of unawareness due to executive dysfunctions has not yet been reported in patients with PD.

Unawareness of deficits appears to be associated not only with damage to cortical brain regions (McGlynn & Kaszniak, 1991; Starkstein et al., 1996), but also with subcortical damage (Godefroy, Rousseaux, Pruvo, Cabaret, & Leys, 1994; Heaton, Navarro, Bressman, & Brust, 1982; Jacome, 1986), in particular anosognosia of dyskinesic movements (Lazzarino & Nicolai, 1991). Few studies have examined the role of unawareness of deficits in PD patients. Starkstein et al. (1996), comparing AD and PD patients on an extensive battery of neuropsychological and psychiatric measures, found a higher level of deficit unawareness among AD patients than PD patients and a disinhibitive syndrome, showing in the AD population a frontotemporal dysfunction of cortical structures. Another study evaluated the unawareness of dyskinesias in PD and Huntington's disease (HD) patients and found that both groups were impaired in detecting the presence of their dyskinesic movements, suggesting that this aspect of anosognosia could be related to subcortical dysfunction (Vitale et al., 2001). In particular, in PD patients the level of unawareness was inversely related to the severity of the dyskinesias, while in HD patients it was directly related to the duration of the disease. However, this study had some important limitations: the parkinsonian patients were not studied on the basis of a neuropsychological and neuropsychiatric assessment, cognitive deterioration was not excluded and no measure of awareness of hypokinetic disorders was considered. Another study (Seltzer, Vasterling, Mathias, & Brennan, 2001), comparing AD and PD patients, showed that the unawareness exhibited by the PD group was more strongly related to neuropsychological dysfunctions, in terms of poor overall cognitive function, especially those assessing memory; in this direction, the authors underlined that PD patients with intact cognitive functions display relatively preserved awareness of motor deficits. In particular, this study demonstrated a correlation between the attention subscale of the Dementia Rating Scale and the discrepancy between patients' and caregivers' evaluations of motor deficit; however, as the authors themselves admit, this can only be considered as weak confirmation of the link between this type of awareness and executive dysfunctions. It is important to underline that the study by Seltzer et al. (2001) did not analyze differences in awareness of motor deficits comparing on and off states and neuropsychological and neuropsychiatric variables in the same patients. Finally, a more recent study (Leritz, Loftis, Crucian, Friedman, & Bowers, 2004) investigating self-awareness of non-demented PD patients showed discrepancies between patients' and caregivers' reports on autonomy in activities of daily living (IADL). In particular, patients described themselves as less impaired compared to caregivers' evaluations of the patients' level of disability. This effect was more pronounced in patients with left-side motor symptoms (greater right basal ganglia dysfunction); the authors concluded that basal ganglia dysfunction might alter insight into the severity of illness more prevalently in patients with right hemisphere lesions. However, even this study did not analyze unawareness of motor deficits by differentiating between motor fluctuations in the on and off states.

From the above considerations, an analysis of the connection between the frontal lobes and the basal ganglia would appear to be a useful model for explaining the presence of unawareness of deficits in subcortical cognitively intact PD patients. With this aim we analyzed the awareness of movement disorders related to pharmacological therapy in the on and off states. We thus expected to find a reduced awareness of hyperkinetic deficits in the on state, associated with the detrimental role of dopaminergic treatment on the prefrontal–subcortical loops producing executive disabilities and a preserved awareness of hypo-bradykinesia in the

off state. We also hypothesized an association between patients' judgments concerning hypokinetic movement disorders and anxiety-depression mood orientation, attesting a preserved awareness of their disabilities during the off state. 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 motor deficits.

2. Methods

2.1. Subjects

Twenty-five patients (13 women, 12 men) with idiopathic Parkinson's disease, motor fluctuations (Hughes, Daniel, Kilford, & Lees, 1992) and receiving levodopa treatment (combined with carbidopa or benserazide), often associated with dopamine agonists, were recruited to participate in the study. The demographic and clinical data of the PD population are summarized in Tables 1 and 2. Patients were enrolled from a series of consecutive out-patients seen at the Neurology Units of the Carlo Besta hospital (Milano, Italy) and the San Luigi Gonzaga hospital (Orbassano, Italy). The inclusion criteria were good clinical response to levodopa with presence of wearing off or on–off phenomena (patients with random on–off were excluded) and peak-of-dose dyskinesias (patients with early morning and painful dystonia were also excluded).

Patients were excluded from the study if they (1) had major depression or dysthymia, based on DSM-IV criteria (1994), (2) had a Mini Mental State Examination score <24 (MMSE, Folstein, Folstein, & McHugh, 1975), (3) had a history of neurological and psychiatric disorders (other than PD), in particular if they had hedonistic homeostatic dysregulation, HHD (Giovannoni, O'Sullivan, Turner, Manson, & Lees, 2000; Pezzella et al., 2003), (5) were taking medications that could directly impact cognitive functioning, other than dopaminergic therapy, such as antidepressants, neuroleptics and anxiolytics, (6) were unable to perform neuropsychological assessment in the off state.

The patients who fulfilled the above criteria were selected for inclusion in the study.

Twenty-five referring spouses and/or caregivers of the PD population took part the study in order to provide information about patients' ability in daily living activities. Collaterals had normal neurological and psychiatric evaluations; mental deterioration was excluded by clinical examination and MMSE. Overall, the caregiver comparison group was demographically similar to the patient group based primarily on socio-economic status. Both patients and caregivers were required to complete the North-Western University Disability Scale, NUDS (Carter, De Latorre, & Mier, 1961), providing an evaluation both in the on and off states.

Patients and caregivers participated willingly in the study and all gave their informed consent. The study was approved by the Ethics Committee of the Department of Psychology, University of Torino.

2.2. Motor, cognitive and neuropsychiatric assessment

PD patients were assessed using an extensive motor, cognitive and psychiatric evaluation. The PD population was also analyzed in terms of side of onset with predominantly right-side or left-side motor symptoms.

Motor screening was performed using the Unified Parkinson Disease Rating Scale (UPDRS, Fahn & Elton, 1987), which was administered by trained clinicians (neurologists) blind to the aim of the study. In particular, parkinsonian motor impairment was

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