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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.

1. Introduction

Levodopa-induced dyskinesias (LIDs) are one of the most common disabling motor complications in advanced Parkinson's disease (PD) (Fabbrini, Brotchie, Grandas, Nomoto, & Goetz, 2007; Jankovic, 2005). LIDs produce greater distress in caregivers (DeBettignies, Mahurin, & Pirozzolo, 1990; Seltzer, Vasterling, Yoder, & Thompson, 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

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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, 2008; Prigatano & Altman, 1990; Stuss & Anderson, 2004; Stuss, Picton, & Alexander, 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, Loftis, Crucian, Friedman, & Bowers, 2004; Maier et al., 2012; 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 & Jahanshahi, 2013; Dujardin, Defebvre, Grunberg, Becquet, & Destée, 2001; Lewis et al., 2012; Muslimovic, Post, Speelman, & Schmand, 2005; Werheid, Koch, Reichert, & Brass, 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, Edelstyn, Stephens, & Ellis, 2009; Maier et al., 2012; 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, Frith, & Wolpert, 2001; 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, Leotta, Bongioanni, & Amanzio, 2014; Palermo, Cauda, 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, 2013; 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