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Research report

Resting-state brain networks in patients with Parkinson's disease and impulse control disorders

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ABSTRACT

Introduction: To investigate intrinsic neural networks connectivity changes in Parkinson's disease (PD) patients with and without impulse control disorders (ICD).
Methods: Fifteen patients with PD with ICD (ICD+), 15 patients with PD without ICD (ICD−) and 24 age and sex-matched healthy controls (HC) were enrolled in the study. To identify patients with and without ICD and/or punding, we used the Minnesota Impulsive Disorders Interview (MIDI) and a clinical interview based on diagnostic criteria for each symptom. All patients underwent a detailed neuropsychological evaluation. Whole brain structural and functional imaging was performed on a 3T GE MR scanner. Statistical analysis of functional data was completed using BrainVoyager QX software. Voxel-based morphometry (VBM) was used to test whether between-group differences in resting-state connectivity were related to structural abnormalities.
Results: The presence of ICD symptoms was associated with an increased connectivity within the salience and default-mode networks, as well as with a decreased connectivity within the central executive network ($p < .05$ corrected). ICD severity was correlated with both salience and default mode networks connectivity changes only in the ICD+ group. VBM analysis did not reveal any statistically significant differences in local grey matter volume between ICD+ and ICD− patients and between all patients and HC ($p < .05$. FWE).
Conclusions: The presence of a disrupted connectivity within the three core neurocognitive networks may be considered as a potential neural correlate of ICD presence in patients

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with PD. Our findings provide additional insights into the mechanisms underlying ICD in PD, confirming the crucial role of an abnormal prefrontal-limbic-striatal homeostasis in their development.

1. Introduction

Impulse control disorders (ICD) can be triggered by dopamine replacement therapies, especially dopamine-agonists, in patients with Parkinson's disease (PD) (Weintraub et al., 2010). Converging evidence (Weintraub, Papey, & Siderowf, 2013) suggest that PD itself does not confer an increased risk for development of ICD in the absence of treatment. On the other hand, only a specific subset of patients with PD will eventually develop ICD under dopaminergic treatment. When an ICD develops, therapeutic management can be very difficult. Therefore, a great deal of effort has gone in the recognition of clinical/pre-clinical, behavioral, neuropsychological and neural correlates of these behavioral symptoms. Several risk factors have been identified, such as younger age at PD onset, male sex, being unmarried, past or current depression, a positive family history of cigarette smoking or substance abuse (Weintraub, David, Evans, Grant, & Stacy, 2015). Moreover, PD patients with ICD seem to present a novelty seeking personality, an inclination for risk-taking behaviors with impaired decision-making and motor inhibition (see for a review Santangelo, Piscopo, Barone, & Vitale, 2017). Previous neuropsychological studies (Santangelo et al., 2009; Vitale et al., 2011) have also demonstrated that ICD in PD are associated with an altered cognitive profile, characterized by impaired cognitive flexibility and planning capability as well as by more inappropriate behavior and poor feedback processes. Evidence from previous brain metabolism (Cilia et al., 2011), functional and morphometric imaging studies (Biundo et al., 2015; Carriere, Lopes, Defebvre, Delmaire, & Dujardin, 2015; Frosini et al., 2010; Rao et al., 2010; Tessitore et al., 2016) have consistently demonstrated a dysfunction within the meso-cortico-limbic-striatal circuit in PD patients with ICD, involving both cortical and subcortical areas which are critical in the reward system, such as anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), insula and ventral striatum (VS). Striatal (Cilia et al., 2011; O'Sullivan et al., 2011; Politis et al., 2013; Steeves et al., 2009) and extrastriatal (Ray et al., 2012) molecular imaging studies have also revealed the presence of an "hyperdopaminergic state" in the brain of PD patients with ICD, when exposed to reward stimuli. However, different task paradigms and controversial findings make the debate about the role of different actors implicated in the pathogenesis of ICD in PD still open. Resting-state fMRI (RS-fMRI) allows for the exploration of brain connectivity between functionally linked cortical regions constituting resting-state networks (RSNs) (Barkhof, Haller, & Rombouts, 2014). Therefore, by means of this fMRI approach it is possible to observe specific disease-related interferences on whole-brain functional connectivity without the potential bias from task-induced brain activations. To date, only one RS-fMRI study (Carriere et al., 2015) has investigated the neural correlates of ICD in PD, mainly focusing on the functional connectivity between striatum and cortical, subcortical regions. Therefore, in the present study we aimed to assess whether the presence of ICD in PD patients may determine abnormalities in the intrinsic neural networks connectivity.

2. Patients and methods

2.1. Study population

We screened consecutive outpatients attending the Movement Disorders Unit of the "Istituto di Diagnosi e Cura Hermitage – Capodimonte" in Naples, Italy. Imaging data were acquired at the MRI Research center of the University of Campania "Luigi Vanvitelli" in Naples, Italy. To be included in the study, the subjects had to meet the following criteria: (1) diagnosis of PD according to the United Kingdom Parkinson's disease Society Brain Bank diagnostic criteria (Hughes, Daniel, Kilford, & Lees, 1992) (2) lack of PD-related dementia according to published clinical criteria (Emre et al., 2007) (3) presence of ICD assessed by means of a modified version of the Minnesota Impulsive Disorders Interview (MIDI) (Weintraub et al., 2006, 2015) and a clinical interview. Exclusion criteria were: clinical signs satisfying criteria of possible atypical parkinsonisms (Wenning, Krismer, & Poewe, 2011); secondary or iatrogenic parkinsonism; cerebral lesions on magnetic resonance imaging and/or computed tomography; severe concomitant diseases that might determine cognitive disturbances or brain metabolic alterations; history of or current psychiatric illness (i.e., hypomanic or manic episodes, psychosis, substance abuse, and attention deficit hyperactivity disorder [ADHD]); use of typical and atypical antipsychotics in the last 2 month prior to enrolment. PD patients without dementia and not affected by ICD (as defined above), and matched to the study group for age, sex and educational level were enrolled as the control group. Moreover, we also recruited a group of healthy age and sex-matched controls (HC). Written informed consent was obtained from all subjects. The study was approved by the ethics committee of the University of Campania "Luigi Vanvitelli", Naples, Italy.

2.2. Procedures

Patients with PD and controls underwent a comprehensive assessment of clinical, neuropsychiatric, neuropsychological functioning, and imaging sessions as described below. Clinical, neuropsychological and imaging assessments were performed in the morning, in the same day, in distinct sessions,