Anhedonia in Parkinson's disease patients with and without pathological gambling: A case-control study

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1. Introduction

Anhedonia refers to the reduced ability to experience pleasure. Operationally, it may be defined as diminished interest or pleasure in response to stimuli usually perceived as rewarding (American Psychiatric Association, 2000). It may be considered both as an enduring personality trait predisposing to the development of schizophrenia and depression, as well as a core symptom of these conditions (Pelizza and Ferrari, 2009). Other studies suggest that anhedonia may be involved in the transition from recreational use to excessive drug intake in patients with substance use disorders (Ahmed and Koob, 1998). From a neurobiological perspective, a central dopaminergic dysfunction has been widely proposed as a neurobiological correlate of anhedonia. The dopaminergic mesolimbic and mesocortical circuits, which comprise the Ventral Tegmental Area (VTA), the ventral striatum, and part of the prefrontal cortex, are activated by rewarding events, behaviors, objects, and physical or emotional states, with the function of ascribing them a positive value. In addition to dopamine, other neurotransmitters mediate the hedonic experience, namely serotonin and endogenous opioids (Kranz et al., 2010).

Compared to controls, anhedonia levels were significantly higher in patients with Parkinson’s Disease (PD), with a prevalence rate of 40% (Isella et al., 2003). Indeed, degenerative changes of the dopaminergic system are not limited to structures regulating motor function but may also involve limbic areas (Boada and Braak, 2000). Several studies (systematically reviewed by Assogna et al., 2011) found anhedonia to be strictly related to depression, apathy and lack of motivation, whereas the relationship between anhedonia and motor symptoms is still unclear.

In the last decade, Pathological Gambling (PG) and other Impulse Control Disorders (ICDs) have emerged as iatrogenic complication associated with Dopaminergic Replacement Treatment (DRT) of PD (Vilas et al., 2012; Raja and Bentivoglio, 2012). The lifetime prevalence of PG in PD patients ranges from 2.2% to 7% (Djamshidian et al., 2011; Santangelo et al., 2013a), and is much higher than in the general population (0.42–2.5%). In recent large

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studies, ICDs were strongly associated with the use of dopamine agonists in general, without associations with specific molecules (Weintraub et al., 2006, 2010; Voon et al., 2011). The occurrence of ICDs in only a subset of PD patients suggests that intrinsic features play a role in their pathogenesis (Raja and Bentivoglio, 2012). Some conditions, such as young age, novelty-seeking traits and alcohol dependence, have been recognized as predisposing factors for the development of ICDs (Pontone et al., 2006; Voon et al., 2007, 2011). Recent studies found an association between the presence of ICDs and psychiatric symptoms (including depressive, obsessive and anxiety symptoms; Voon et al., 2011). Inconsistent results have been reported on cognitive impairments (Santangelo et al., 2009b; Siri et al., 2010; Vitale et al., 2011; Bentivoglio et al., 2013), mainly related to frontal lobe dysfunction (ventral frontotriatal networks; Santangelo et al., 2009b; Bentivoglio et al., 2013). On this basis, it has been suggested that PG and other ICDs are behavioral symptoms that might arise from a top-down dysregulation of behavior, and that differences among subtypes of ICDs may reflect differential involvement of the neural substrates devoted to process intrinsic (i.e., sex and eating) or learned rewards (i.e., money; Vitale et al., 2011; Santangelo et al., 2013b).

ICDs in the general population have epidemiological and phenomenological overlaps with substance addiction, leading to their classification as behavioral addictions (Potenza, 2008). Given that in substance use disorder patients anhedonia is part of the abstinence symptomatology (Martinotti et al., 2008b) and has been found to be an important factor in precipitating relapse (Hatzigiakoumis et al., 2011; Koob and Le Moal, 2001), the aim of the present study was to test the hypothesis that some psychiatric traits, and particularly anhedonic features, might be associated with the development of PG and other ICDs in PD patients.

### 2. Materials and methods

We included 154 consecutive out-patients with a diagnosis of PD according to UK Brain Bank criteria (Gebel et al., 1999), seen at the Movement Disorders clinic of the “A. Gemelli” Hospital in Rome, Italy from March to September 2011. Exclusion criteria were: any history of neurological illness other than PD; possible or probable dementia according to clinical diagnostic criteria (Emre et al., 2007); mental retardation; inability to provide an informed consent. In order to test the real impact of the anhedonic dimension on behavioral addictions and ICDs occurring in PD patients, we did not exclude patients affected by major depressive disorder, as diagnosed according to DSM-IV criteria.

Demographic and clinical information (age at onset, disease duration, side of symptoms’ onset, educational level and daily medications) was recorded. All patients underwent a clinical evaluation, including Unified Parkinson’s Disease Rating Scale motor score (UPDRS III), Hoehn and Yahr stage, motor complications of therapy and a clinical interview in which sleep history was gathered to assess the presence of REM behavioral disorder – RBBD – before and after PD diagnosis (Neukrug and Anclol-Israel, 2012). We administered a battery of neuropsychological tests, including: Mini Mental State Examination (MMSE) in order to evaluate general cognitive abilities, and Frontal Assessment Battery (FAB) to evaluate frontal lobe functions (Dubois et al., 2000).

The psychiatric evaluation included: Snath–Hamilion Pleasure Scale (SHAPS), Barratt Impulsiveness Scale Version 11 (BIS-11), Hamilton Depression Rating Scale (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A). SHAPS (Snath et al., 1995) is a 14 items scale to assess anhedonia in different psychiatric conditions, specifically validated for detection of anhedonia in PD patients (Santangelo et al., 2009a); a score ≥ 3 indicates a reduction of hedonic abilities. The scale showed a satisfactory internal consistency (α=0.837). BIS-11 (Patton et al., 1995) assesses impulsivity traits (α=0.79; Fossati et al., 2001) and identifies three subtypes of impulsivity: motor impulsivity, non-planning impulsivity and attentional impulsivity. Hamilton Depression Rating Scale (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A) assess depressive symptoms and anxiety, respectively (Hamilton, 1959, 1960). Raters MP and GL were specifically trained and showed a good inter-rater reliability on all instruments (k 0.80).

All patients also underwent a psychiatric interview. PG was diagnosed according to DSM-IV criteria (American Psychiatric Association, 2000). Other ICDs were also assessed: hypersexuality according to Voon et al.’s criteria (2006); Compulsive Shopping according to McGlroy et al.’s criteria (1994); Binge Eating according to DSM IV; Punding, according to the Punding Rating Scale (Fasano and Petrovic, 2010); Hedonistic Homeostatic Dysregulation according to criteria proposed by Giovannini et al. (2000).

Patients were tested in the morning during their “medication-on” condition. They all agreed to enter the study and sign a consent form according to the Declaration of Helsinki.

#### 3. Results

Thirty-four out of the 154 PD patients (22.1%) included in the study fulfilled the diagnostic criteria for the co-occurrence of ICDs (Table 1). Twenty-four patients had a single ICD, while 10 patients showed multiple ICDs (two ICDs, n=9; three ICDs, n=1). Eleven fulfilled the diagnostic criteria for PG (7.1%). Twenty-three patients had other ICDs: hypersexuality (n=20; 13%), binge eating (n=9; 5.8%), and compulsive shopping (n=5; 3.2%). The remaining 120 patients did not report any ICDs. Table 2 lists the demographic and clinical features of patients according to the presence or absence of PG and other ICDs: no between-group significant differences emerged.

Compared to other ICDs group and PD controls, patients with PG scored significantly lower on the FAB, had higher levels of impulsivity, higher SHAPS scores, and higher incidence of anhedonia (45% in PG patients, vs. 9% in ICDs, vs. 14% in PD controls; $\chi^2=8.02$, $p<0.05$). No other significant differences emerged when comparing groups, in particular comorbid depressive disorders and anxiety disorders were comparable across groups (Table 3).

Table 4 displays significant correlates of PG using multivariate logistic regression. The overall model exhibited a good fit with the data ($\chi^2=15.65$, $p<0.001$, pseudo R-square=0.24). Three variables were statistically significant predictors of PG: presence of anhedonia, impulsivity levels (as measured by BIS-11) and degree of frontal lobe dysfunction (as measured by FAB scores).

### 4. Discussion

The present study assessed the occurrence of anhedonia in PD patients with and without PG. In our series, 45% of PG patients were anhedonic, a significantly higher incidence than in PD patients.
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