Non-motor symptoms in Parkinson’s disease.

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Abstract

Parkinson's disease (PD) includes motorial and non-motorial features, both negatively influencing patients' life quality. While motor symptoms are well recognized and described, non motor symptoms are becoming a more recent focus of interest and research. This review aims to give an updated information about non-motor symptoms in PD. It comprehends three sections: 1) cognitive dysfunctions, 2) impulse control disorders and 3) emotional aspects. Articles from 2008 to 2013 were researched through the following keywords: non-motor symptoms in PD, cognitive disorders in PD, Parkinson's disease screening test, impulse control disorders in PD, neuropsychiatric disorders in PD, depression and apathy in PD. Cognitive impairments of PD subjects include the executive, attentional and visuospatial functions and are frequently associated with depression, anxiety and impulse control disorders (ICD). Hyper-sexuality, compulsive shopping, compulsive overeating, punding and pathological gambling are the most frequent ICD. PD is an insidious and multifaceted disease. Motor symptoms may only represent the tip of a massive iceberg where the hidden part consists of behavioural, cognitive and emotional symptoms. Some of these manifestations are intrinsic to PD while others are related to therapies. An early diagnosis of both motor and non-motor symptoms is hence desirable. The knowledge of these aspects may contribute to the development of novel treatment options in a multidimensional approach.

Keywords: PD, non-motor symptoms, impulse control disorders, mood disorders, and cognitive disorders.

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Introduction

Parkinson’s disease (PD) is the second most frequent neuro-degenerative disease [1]. It affects over 4 million people annually and the number is forecasted to become double in the next 20 years [2].

PD symptoms include motorial and non motorial features. The motor features essentially consist of rigidity, bradykinesia and postural instability, while the non-motor features include different behavioral aspects [3]. Currently, the diagnostic criteria of PD are exclusively based on the specific motor symptoms, mainly related to substantia nigra pathology. Motor heterogeneity of PD is well established, while the clinical differentiation based on the non-motor symptoms has not been clearly established yet. This review aims to give an updated information on the most common non-motor symptoms in Parkinson's disease of which depression, anxiety and impulse control disorders (ICD). Hyper-sexuality, compulsive shopping, compulsive overeating, punding and pathological gambling are the most frequent ICD. PD is an insidious and multifaceted disease. Motor symptoms may only represent the tip of a massive iceberg where the hidden part consists of behavioural, cognitive and emotional symptoms. Some of these manifestations are intrinsic to PD while others are related to therapies. An early diagnosis of both motor and non-motor symptoms is hence desirable. The knowledge of these aspects may contribute to the development of novel treatment options in a multidimensional approach.
quality of life. Non-motor symptoms of PD also include cognitive disorders that can progressively lead to dementia. These cognitive deficits, that have become only recently a focus of attention, are grouped as ‘Mild Cognitive Impairment in PD’, and represent an intermediate state between the normal cognition and dementia. They occur in about 20% - 50% of all cases of PD patients and concern the executive, attention and visuospatial functions.

Methods

A systematic literature search was conducted on popular search engines (including PubMed). Articles from 2008 to 2013 were researched through the following keywords: non-motor symptoms in Parkinson's disease, cognitive disorders in Parkinson's disease, Parkinson's disease screening test, Impulse control disorders in Parkinson's disease, neuropsychiatric disorders in Parkinson's disease, depression and apathy in Parkinson’s disease, anxiety in Parkinson disease. We divided the review into three sections: the first concerning cognitive deficits in PD and how they can be investigated and measured, the second is about the impulse control disorders while the third focuses on the emotional aspects which is about anxiety, depression and apathy.

Results and Discussion

Results and discussion are divided in three parts (1, 2 and 3):

Cognitive disorders in Parkinson's disease

The concept of mild cognitive impairment

Today cognitive impairment is increasingly recognized as part of PD non-motor features. Mild cognitive impairment (MCI), introduced in the late 1980’s, represents a degree of cognitive impairment that is not normal for age and, even if it may progress to dementia, is not fulfilling the criteria for dementia diagnosis. The concept of MCI has evolved from its initial use. First criteria for MCI, as put forth by Petersen et al [4], are that the cognitive decline is related only to memory. These criteria were subsequently revised by Winblad et al. [5] to incorporate both amnestic and non-amnestic clinical phenotypes of MCI. The revised criteria established that: 1) presence of a cognitive complaint, which was not normal for age and represented a decline in cognitive function, but did not represent dementia or impair functional activities, 2) presence of memory impairment (i.e. categorized as yes or no), and thereby as amnestic or non-amnestic MCI, respectively, and 3) number of domains impaired (i.e. single or multiple), thereby leading to 4 MCI subtypes:
• amnestic MCI single domain
• non-amnestic MCI single domain
• amnestic MCI multiple domain
• non-amnestic MCI multiple domain

The concept of MCI implies that there is a continuum from normal cognition to dementia, with MCI representing a transitional or prodromal state. Cognitive impairment has been frequently reported in non-demented PD [6, 7]. The mild cognitive impairment in Parkinson's disease (PD-MCI) may represent an intermediate state between normal cognition and dementia in Parkinson's disease [4].

The presence of cognitive deficits in non-demented PD has been recognized for a few years. Only recently the idea has emerged and operational definitions have been proposed. MCI can occur in 20% - 50% of cases in patients with Parkinson's disease; PD-MCI (2). The PD-MCI patients generally are non-amnesic, have cognitive deficits of executive function, attention and visual-spatial function (even if the cognitive phenotype of PD-MCI is heterogeneous a small percentage of patients show greater amnesic deficit compared to other cognitive domains) (2). However, single domain impairment with non-amnestic deficits predominates in PD-MCI.

Typical features of PD-MCI include slow processing, difficulty with multi-tasking or planning, decreased attention and concentration, and interrupted word finding in a task. PD-MCI patients are characterized by a reduced visuospatial, visuoperceptive or visuoconstructive ability, although some studies do not observe this [8, 9]. The function of language is relatively spared in non-demented PD patients. However, decreased vocabulary in spontaneous speech, reduced understanding of complex phrases, and reduced verbal fluency may occur, which reflects the involvement of the frontal lobe. (10). As for memory, PD patients show difficulty in learning new information, as demonstrated by impaired performance in tests of free recall, but these patients improve with semantic cues or recognition tasks [11,12]. The difficulty in recording and retrieval of information may derive from executive dysfunction rather than encoding deficits, although some studies also show deficits in the encoding [13].

Furthermore some PD-MCI patients show bradypsychia or slowing of psychomotor speed in neuropsychiological tests. In summary the most compromised is the executive function [14]. Non-amnestic single domain that predominate in PD-MCI is the executive function which includes the ability to plan, organize, initiate and regulate goal-directed behavior, which is based on frontal-striatal circuit including prefrontal regions, such as the dorso-lateral prefrontal cortex and its connections with the basal ganglia. Some research however, appears to contradict
Non-motor symptoms in Parkinson’s disease

The results of this research show that the cognitive profile of PD-MCI is heterogeneous with a mix of non-amnestic and amnestic deficits and single and multiple-domains. A reason for this is that each recruit several population studies of patients with PD (i.e., definition of PD-MCI with different criteria), and use different neuropsychological tests, cut-off scores and sources of normative data. Furthermore, currently the population of PD-MCI patients is very small. Therefore, it signifies the difficulty of identifying subtypes of MCI with a very small number of patients. Till recently, according to the most evaluated studies of PD-MCI patients, 58% showed single domain MCI (34% and 24% with frontostriatal deficit in the temporal lobe) and 48% of cases showed multidomain cognitive deficit [6].

Operational definitions of PD-MCI are currently in progress. However most studies use the following [8]:
1) compromise of one or more cognitive domains,
2) no impairment in daily life,
3) general cognitive abilities in the normal range I.

The following issues are to be taken into account:

- The availability of subjective and objective data from sources including the patients, informants, clinical and neuropsychological tests.
- The evaluation of daily life abilities in subjects having some physical limits.
- The presence of co-morbid depression, anxiety, apathy, fatigue, psychosis, sleep disorders and their impact on the neuropsychological tests.
- The absence of tests defined for some specific functions, and cut-off scores.
- The impact of being in the "on" or "off" phase during test administration.
- The motor activities required by the test.
- The effect of mood disorders, psychosis, fatigue and sleepiness during neuropsychological tests.

The perception of the cognitive impairment by patients and their caregivers, may not be entirely reliable [15, 16, 17], as it is difficult to separate the cognitive difficulties from the motor limitations. Thus, information from several sources (e.g., patient, caregiver, and clinician) is required to determine whether the patient has a true cognitive decline or not. In addition, PD-MCI studies vary regarding the evaluation of daily activities. This issue is particularly challenging, since daily activities may be profoundly affected by the motor symptoms. So specific measures that can distinguish the cognitive from the motor aspects in daily activities are needed [18]. The cognitive performance may also differ in the "on" and "off" phase, particularly in the executive function tests; patients with motor fluctuations may also behave differently [19, 20]. Neuropsychological tests requiring a performance within a definite period of time, or requiring specific motorial activities may also put a further challenge in these patients. Non-motor features such as depression, anxiety, apathy, psychosis, fatigue, and sleep disorders are common in Parkinson's disease, particularly in patients with cognitive impairment or dementia [14, 5]. These non-motor signs, which are typical of Parkinson's disease, can significantly interfere with the cognitive testing performance and hence have to be carefully considered. Increased appreciation of the importance and profound impact of non-motor complications in PD, as well as MCI criteria (discussed above), have helped pave the way for PD-MCI research. Studies suggest that PD-MCI can represent the first stage of the cognitive decline, and that they represent a risk factor for the development of dementia in PD subjects [21, 14].

Parkinson disease dementia (PDD)

One of the main reasons for the development of MCI reach and criteria has been the early identification of patients who are at risk of converting to dementia. PD-MCI has been associated with older age at evaluation, older age at PD onset, male gender, depression, more severe motor symptoms, and advanced disease [22]. However, compared to PD subjects without MCI [7] no significant differences have been found in the demographic or the motor features of PD-MCI. Larger sample sizes of PD-MCI and longitudinal follow-up studies in PD-MCI patients will permit the examination of the different MCI subtypes, their progression and risk factors for conversion to PDD. Few studies have evaluated the progression of PD-MCIPD-MCI patients to dementia. Some longitudinal studies report that dementia occurs in the majority of the patients and is found in 78% of all cases after 8 years of having the disease [23]; and in 83% of the cases after 20 yrs [3]. Another study [7,24] showed that 62% of the PD-MCI subjects, after 4 years, converted to PD dementia (PDD) [21]. The single domain non-amnesic MCI was associated with conversion to PDD, whereas predominant amnesic deficits and MCI multiple domains were not, however the sample size was small and the neuropsychological battery limited. In this cohort, the patients who developed dementia also had higher scores in the Beck Depression Inventory. The predictors of global cognitive decline included a more posterior cortical profile (e.g., impaired semantic fluency or pentagon copying) and the non-tremor dominant motor phenotype at baseline. The cognitive profile of PDD patients usually reflects a 'subcortical dementia' syndrome with the non amnesic pattern and with a greater impairment of the executive functions. Attention, and visuospatial function are then more impaired than declarative memory, language and praxis [25]. Studies also suggest that not only the frontostriatal dysfunctions contribute to the cognitive impairment, but that some posterior cortical deficits may contribute to the risk of conversion to PDD. In 2007, the Movement Disorder...
Society (MDS) task force proposed some diagnostic criteria for PDD. According to MDS-PDD, in contrast to DSM-IV criteria [26], the memory impairment is not important, rather, the more important criteria are the non-amnesic cognitive domain and the presence of concomitant behavioral features (e.g., apathy, mood disturbances, psychosis). The cognitive characteristics of PDD, however, may be heterogeneous, and some patients may experience more "cortical" profiles with disorders of memory and language. Risk factors for PDD include mild cognitive impairment and cognitive dysfunction at baseline. Other factors, such as age, the long duration of Parkinson's disease, the age at the disease onset, and the severity of the motor signs, as well as the akinetic phenotype, psychosis, depression, and genetic factors (as APOE), have been associated with an increased risk of PDD [27, 28].

**Screening Test**

Several global cognitive scales have been proposed as screening tests for PD-MCI and/or PDD, including the MoCA, SCOPA-COG, Parkinson Neuropsychometric Dementia Assessment (PANDA), PD-Cognitive Rating Scale (PD-CRS). The MoCA, which was originally developed to screen for MCI in the general population, assesses orientation, executive function, attention/concentration, naming, verbal abstraction, and visuocognitive constructiveness. Although the MoCA is more helpful in detecting PDD, the SCOPA-COG; which includes tests for nonverbal and verbal memory, attention, executive function, verbal fluency, and visuospatial function, is reliable and sensitive to PD cognitive deficits [29]. The PANDA which includes tests for immediate and delayed recall memory, alternating verbal fluency, visuospatial abilities, and working memory/attention has been reported to discriminate between PDD, PD-MCI, non-demented PD, and controls [30]. Although the established MCI criteria do not specify how many neuropsychological tests or which tests should be used, what cognitive domains and how many should be examined, what normative data should be used, or which cut-off scores should be employed. A good screening test is an important consideration in the diagnosis of PD-MCI and in the development of operational definitions.

**Pathogenesis**

Cognitive deficits in non-demented PD have been frequently attributed to neurochemical alterations in dopaminergic, cholinergic, and other systems and neuro-pathological contributions of limbic and cortical Lewy bodies and neurites, amyloid deposition, neurofibrillary tangles, and cerebrovascular disease. Extensive literature has highlighted the relationships between executive function and dopamine. Dopaminergic medications such as levodopa or dopamine agonists may have variable effects on cognition, with improvement in executive function tasks in some PD patients while worsening in others, or no effect [31]. Cognitive deficits in non-demented PD patients have often been attributed to neurochemical alterations in not only dopamine districts but also in the cholinergic domains (the latter mainly involves deficits in attention, learning and memory). Executive dysfunction may reflect the impairment of the frontal lobe, concerning in particular, the dorsolateral prefrontal cortex dysfunction and disruptions resulting from frontostriatal loop due to the degeneration of the nigrostriatal or mesocortical dopaminergic pathways [6]. Executive dysfunction has been associated with decreased mental flexibility, and impaired working memory [32, 33]. Dopaminergic medications may improve some neuropsychological measures in PD patients such as non-specific effects on alertness/arousal, working memory, planning tasks, cognitive flexibility, and apathy [19, 31, 34]. The cognitive effects of dopaminergic therapies, however, are highly variable in PD as some patients show either worsened reversal learning, decision-making, or choice reaction times or show no effect on cognitive slowing [31,35]. Besides dopamine, the cholinergic system has been implicated in PD-related cognitive impairment with degeneration of the nucleus basalis of Meynert, decreased cholinergic activity in the cortex, and reduced choline acetyltransferase activity in the frontal and temporal lobes [36,37]. These deficits may be linked to impairment in attention, learning and memory in PD. Today symptomatic treatments of PD-MCI and PDD are limited and there are no established neuroprotective interventions. Cholinesterase inhibitors and memantine in PDD provide a modest benefit, and only rivastigmine has been approved by the Food and Drug Administration in the United States for PDD [2].

**Impulse control disorders in Parkinson’s disease.**

The prevalence of psychiatric disorders in patients with PD varies from about 12 to 90%. This high comorbidity is likely to reflect the changes that occur in complex functional circuits that include the basal ganglia, thalamus, limbic structures and the prefrontal cortex. Among the psychiatric manifestations of PD, we can distinguish those independent of drug therapy, such as depression and anxiety disorders, and those most likely caused by the interaction between the clinical characteristics of patients and dopaminergic therapy, such as disorders of impulse control and psychosis. The prevalence of impulse control disorder (ICD) is reported with increasing frequency in patients with PD [38, 39]. ICDs are characterized by the inability to resist an impulse to act, resulting in the impediment of individual and social welfare.

These abnormal behaviors may endanger the activities of the daily life of the subject and have a negative impact on their caregivers and families [40]. ICDs in PD are often under-reported by patients and little investigated by physicians [41]. The factors associated with ICDs in PD
are: young age, marital status, a family history of impulse control disorders, the duration of the disease, early onset of the disease, akinetic-rigid PD and treatment with levodopa [42, 43, 44, 45, 46, 47, 48, 49]. ICDs most commonly reported in the literature are: pathological gambling (PG), hypersexuality (HS), compulsive shopping, compulsive overeating [41], and stereotyped behavior (punding). Some studies make a difference between ‘impulsive’ and ‘compulsive’ disorders in PD: at the two ends of this continuum we can place the punding at one side and all the other (gambling, compulsive shopping and hypersexuality) at the opposite side, compulsive overeating is inserted in an intermediate position. Impulsivity can be defined as a predisposition to react quickly and not reflectively to internal or external stimuli without adequate consideration of possible negative consequences [50]. Compulsivity is the overwhelming tendency to perform stereotyped, repetitive acts that interfere with everyday activities [51]. ICDs from the neurobiological perspective can be explained as the result of a bottom-up hyperactivity of some networks of the striatum and contemporary hypoactivity of cortex areas connected to those networks. As results the inhibitory top-down control is insufficient. While impulsivity would be the result of an abnormal activation of the circuit consisting of the ventral striatum / nucleus accumbens, amygdala and medial orbitofrontal cortex, compulsivity instead could be explained as the result of disorders of dorsolateral striatum and frontoparietal cortex [52].

**Gambling**

Pathological gambling is defined according to the DSM IV criteria, such as the inability of the patient to resist the impulse of the game despite important consequences on their personal, family or employment life. The prevalence of gambling in PD is approximately 7% compared to a prevalence of approximately 1% in the general population [53] (Table 1). In most subjects with PD, gambling is associated with dopamine-agonist therapy. For example, in some studies it is reported that the oral administration of pramipexole may induce a greater degree of gambling compared to other medications for its disproportionate stimulation of dopamine D3 receptors. Gambling associated with levodopa mono-therapy is rare. From the neuropsychological perspective, it has been associated with a dysfunction of the executive functions [54]. Shapiro et al reported the most common gambling are to the slot machine (70%) followed by scratch cards (50%), card game (40%), lottery (30%), casino (30% ), horse racing (20%) [55]. Previous studies have suggested that the proximity of home to casino can contribute to the development of pathological gambling in patients with PD [56]. The onset of PD at a young age, male sex, novelty seeking personality, anxious and / or impulsive personality, a history of alcohol abuse are significant predictors of gambling. Most of the family members of individuals with PD attribute the pulse of the game to the personality of the patient, but it is important to inform family members that the abnormal behavior is related to the disease [57].

**Hypersexuality**

Hypersexuality is a syndrome characterized by the need of frequent sexual experiences, or by polarization of thoughts on recurrent and intense sexual fantasies, negatively interfering with daily life. The person has excessive sexual behavior and commits too much money, time, concentration and energy to the topic. The patient describes his behaviour as out. Sometimes paraphilic behaviours such as, exhibitionism, voyeurism etc. may occur. The prevalence of hypersexuality was found in 2-3.5% of PD patients [39, 42]. This disorder is associated with administration of levodopa or familiar psychiatric or cognitive deficits [58]. Increased sexual desire is reported by 8.8% of patients with PD or by their caregivers [59]. It can often hamper the relationship with their partners and can also cause problems in the working environment. Hypersexuality in PD is associated with the male gender, earlier onset of the disease, treatment with dopamine agonists and with a history of depression [60, 61]. Patients with hypersexuality more often have general cognitive impairment, in particular, they obtain lower scores on tests of verbal learning and inhibitory control (Stroop Test) compared to PD patients with gambling and compulsive eating [59]. Some authors believe that the interruption of dopamine is consistently effective in treating patients with hypersexuality [39, 58].

**Compulsive Shopping**

Compulsive shopping is the uncontrollable desire to shop. Negative feelings such as sadness, loneliness, frustration or anger increase the tendency to make purchases, while the act of buying is associated with pleasant emotions such as happiness, a sense of power and competence (retail therapy). However, purchase becomes a disease when the money invested for shopping is excessive in relation to the economic possibilities of the subject, when purchases are repeated several times a week, when the goal of shopping is not to buy something useful but to buy in order to satisfy a disturbing need that drives the person to walk into a store and pick up anything. The purchase brings a sense of reduction of tension, but becomes reinforcement for the repetition of dysfunctional behavior. Failure to purchase causes anxiety and frustration. The prevalence of this disorder is estimated to about 0.4-2% [39, 42, 45]. In a recent study, compulsive shopping was present in 6% of patients with PD and is related to high doses of dopamine [62]. It is more common in women and mainly results in the accumulation of useless unnecessary objects [63]. It is a disabling disorder that may break the family balance and / or sell all of one’s assets without the knowledge of their partner.
Compulsive overeating

The American Psychiatric Association defines binge eating disorder (BED) as eating an amount of food that is definitely larger than most people would eat during the same period of time, under similar circumstances, coupled with a perceived lack of control over one’s eating (Criterion A). Patients with BED must exhibit marked distress regarding binge eating (Criterion C) and 3 out of 5 associated features (Criterion B: 1. Eating until feeling uncomfortably full. 2. Eating large amounts of food when not physically hungry. 3. Eating much more rapidly than normal. 4. Eating alone because you are embarrassed by how much you're eating. 5. Feeling disgusted, depressed, or guilty after overeating).

Binge eating episodes must occur at least twice weekly for six month (Criterion D), and individuals must not engage in inappropriate compensatory behaviors such as purging or fasting (Criterion E) [64]. Many researchers have recently supported the consideration of subthreshold eating disorders in the case of individuals who fail to meet all of the above DSM-IV criteria [65]. The true prevalence of this disorder is unknown, although it has been reported in up to 4.3% of the cases and is more common in females [41, 45, 66]. Overeating severity was correlated with measures of impulsivity and mania. Overeaters met psychometric criteria for at least one other ICD, this overlap is consistent with the current view of a common pathophysiological mechanism underlying these behaviors in PD involving mesocorticolimbic sensitization. Multiple studies have implicated dopamine agonists acting on D3 receptors in the pathophysiology of ICDs and compulsive overeating in PD [49, 67]. A study identified a history of subthalamic nucleus (STN) Deep Brain Stimulation (DBS) surgery as the only significant predictor of binge eating with an increase of desire for sweets (i.e., candies and ice cream) in a non-selected sample of consecutive PD patients without any psychiatric disturbance prior to surgery [68]. The relatively high prevalence of clinical and subclinical symptomatology reported here suggests that physicians should be aware of binge eating in their PD patients, especially considering the potential adverse consequences of prolonged occurrences for example hypertension, diabetes, hypercholesterolemia.

Punding

Stereotypical behaviour or punding consist of automatic, purposeless, motor rituals that are not associated with compulsion. They are generally related to previous hobbies and are accompanied by a subjective feeling of fascination and pleasure: cleaning activities, assembling and disassembling objects, gardening tasks, writing or drawing, etc. The motor activities of patient with punding are generally fairly useless, unrelated to compulsion, and provide the patient with a great nonproductive, exaggerated and often inappropriate fascination. These activities vary and include handling, storing, ordering, classifying, or repeated, stereotypically, and purposelessly assembling and disassembling objects [38, 39, 42, 44, 47]. These activities are performed by the patients during most of the day and even interfere with everyday activities. Nonetheless, neither the patients nor their caregivers have reported ‘punding’, probably because they did not attribute it to PD. Inversely they interpreted these behaviors as the consequences of patient’s hyperactivity. Punding is unassociated with psychotic or affective symptoms, and it is not related to obsessive thoughts or cognitive impairment. Other characteristics, which may be more common among punders, include a higher severity of dyskinesia, younger age of disease onset, longer disease duration, and male gender [68]. Prevalence varies greatly (between 0.34 to 14%), but in literature there are large disparities in study populations, assessment methods, and criteria [69]. In one prospective study, punding is detected in 14% of PD patients (17 out of 123 patients), although it may go up to 34% (17 out of 50 subjects) in patients with PD who are under treatment with levodopa-equivalent drugs, in doses exceeding 800 mg/day [70]. A recent study observed an association between punding, dopaminergic medications, and impulse control disorders.

Table 1. Prevalence of ICD

<table>
<thead>
<tr>
<th>ICD</th>
<th>Definition</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td>Gambling</td>
<td>Inability to resist the impulse despite drastic consequences</td>
<td>1 - 7%</td>
</tr>
<tr>
<td>Hypersexuality</td>
<td>Need of frequent sexual experiences. Polarization of thoughts on recurrent and intense sexual fantasies that negatively interfere with daily life</td>
<td>2 – 3.5%</td>
</tr>
<tr>
<td>Compulsive Shopping</td>
<td>Uncontrollable desire to shop</td>
<td>0.4 - 2%</td>
</tr>
<tr>
<td>Compulsive overeating</td>
<td>Eating an amount of food that is definitely larger than most people would eat during the same period of time under similar circumstances coupled with a perceived lack of control over one’s eating.</td>
<td>4.3%</td>
</tr>
<tr>
<td>Punding</td>
<td>Stereotypical behaviours consisting of automatic, purposeless, motor rituals that are not associated with compulsions; they are generally related to previous hobbies and are accompanied by a subjective feeling of fascination and pleasure</td>
<td>0.34 - 14%</td>
</tr>
</tbody>
</table>
Emotions in Parkinson’s disease

Changes in emotions in a person can have different causes such as, hormonal changes and alterations at the levels of neurotransmitters and in the autonomic nervous system. The most visible changes are in the facial expressions, gestures and postures in response to internal (thoughts, memories, etc) or external stimuli.

Although, the study and the neuroanatomy of emotional processes are quite difficult, it is now known that the amygdala, the basal ganglia and the dopaminergic system are deeply involved in these processes. These aspects are often clearly altered in patients with PD. The study of emotional processing in PD can improve the understanding of disease correlations and neuropsychology of emotions.

Numerous studies on Parkinson’s disease have investigated the reactions to different stimuli (negative, positive and neutral); while others have studied the intensity of the responses of PD patients as compared to healthy subjects. It is found that PD patients have generally less emotional responses than healthy subjects, especially to aversive stimuli [71]. This condition is perhaps due to reduced activation of the amygdala that is intensively involved in the experience of fear [72]. According to many authors, the minor activation would be at the basis of alexithymia (inability to identify and describe one's feelings, and to distinguish between feelings and bodily sensations of emotional arousal) that is observed in many PD patients. According to recent studies, it is not considered a consequence of depression [73], instead, it is a depression-independent phenomenon that may be associated to the processes of the disease [74].

PD patients also have difficulty in recognising facial expressions [75] and prosodics. The major hypothesis is that, not only is such recognition objectively difficult [76], but above all, it derives from mechanisms involving the basal ganglia which is known to be a dysfunctional structure in PD [77]. Peron et al [78] suggest that the deficits of recognition are also explained by a reduced activation of the amygdala [79, 80] and alterations of dopaminergic pathways. A study by Lawrence et al. demonstrated that the emotional facial expressions of anger were diminished after the administration of a dopaminergic antagonist [81].

Moreover, the progress of the disease and the ‘facies amimica’ causes difficulties in automatic emotional expressions (for a damage to the pyramidal tract and the Basal Ganglia network), while the difficulties of voluntary production of facial expressions would be lower [82]. The data are conflicting. However, about 30 years ago researchers have elaborated the simulation theory: the deficit in the production of facial and vocal emotional expressions, explains, the deficit in emotion recognition processes in PD [83].

Recently the dysprosody in PD patients has gained great importance. Many authors have misinterpreted it as a mere disorder of the motor/articulatory system [84] and much later has it been recognized as an emotional disorder [85]. A recent study shows a compromise of these two sides: the alterations of emotional processing contribute to speech changes in PD especially the emotional prosody in addition to motor impairment [86].

Anxiety and Parkinson’s disease

About 40% of patients with Parkinson's disease (PD) suffer from anxiety disorders according to the classification of DSM IV [87]. According to this manual, the anxiety disorders include: panic disorder with and without agoraphobia, generalized anxiety disorders, obsessive-compulsive disorder, social phobia, post-traumatic stress disorder and acute stress disorder [26]. Virtually all the types of anxiety disorders have been described in PD but the panic disorder and social phobia appear to be the ones most commonly encountered.

The above-mentioned disorders have a tremendous impact on the quality of life of PD patients despite being under-estimated or misdiagnosed [88]. It is believed that these symptoms are not just a consequence linked to the awareness of the disease, because the occurrence of anxiety disorders in PD patients is far more prevalent than in the general population or in those with other chronic diseases [89].

However, other studies consider these disorders as a side effect due to the treatment of motor disorders [90] contrary to those data that report cases of onset of anxiety symptoms even before that of the motor symptoms [91,92]. Moreover, it seems that the anxiety disorders decreased with age as young onset PD patients, are more likely to experience anxiety than the late onset subjects. On the other hand, some researchers found that there is a correlation between anxiety symptoms and stages of PD. It is uncertain whether anxiety is a reaction to worsening of motor symptoms or the two classes of symptoms share a common dopaminergic substrate [87].

The reason for the high frequency of anxiety in Parkinson's disease is poorly understood. The degeneration of neurotransmitter systems and the dopamine might play a specific role in the occurrence of these affective disorders. Remy et al. [93] used positron emission tomography (PET) and an in vivo marker of dopamine and norepinephrine transporter-binding to
examine depression and anxiety in PD. Their results suggest that these symptoms are associated with loss of dopaminergic and noradrenergic innervation in the limbic system [93].

Depression and Parkinsonism
Previous research has suggested that depression is relatively common among individuals with Parkinson’s Disease (PD): about 40% of individuals with PD experience, in fact, some form of depression [94].

The DSM-IV requires at least 5 symptoms for diagnosis [26]:
- depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful);
- markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others);
- significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day;
- insomnia or hypersomnia nearly every day;
- psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down);
- fatigue or loss of energy nearly every day;
- feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick);
- diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others);
- recurrent thoughts of death (not just fear of dying), and recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

The depression is often under-diagnosed [95], since many symptoms are also those typical of PD (weight loss, fatigue or loss of energy, decrease in appetite, etc.). Therefore the use of rating scales may support a correct and early diagnosis [96] and it may help the patients to know their condition [97]. There are many valid scales such as the Hamilton Depression Rating Scale (HDRS), the Beck Depression Inventory (BDI) and the Geriatric Depression Scale (GDS) but it requires training for administration and evaluation of the responses [98, 99,100].

A recent review, which compared the characteristics of 9 depression rating scales, indicated that the GDS is the most valid one for its brevity, favorable psychometric properties, and lack of copyright protection [101]. The diagnosis is still a major problem, therefore the National Institute of Neurologic Diseases and Stroke (NINDS) and the National Institute of Mental Health (NIMH) tried to review the diagnostic criteria of the depression. The research group did not yield definitive answers but are making great strides in this direction.

Counseling or psychotherapy can be helpful but it is generally believed that depression is both psychological and organic in PD; therefore, treatment with medication is often required. Early randomized studies of antidepressants for the treatment of depression in PD included the tricyclic antidepressants (TCAs), amitriptyline and nortriptyline and the selective serotonin reuptake inhibitors (SSRIs) citalopram and fluvoxamine. A Cochrane review summarized these randomized studies, and found insufficient data to determine efficacy and safety of these antidepressants [102]. However, antiparkinson drugs might have beneficial effects not only on the motor symptoms of disease, but also on patient's mood [103].

The depression often appears before the motor symptoms [103], and it is not yet clear whether it is an early symptom or perhaps even a risk factor [104]. However it is clear, at least from the positron emission tomography (PET) studies, that hypometabolism and catecholamine abnormalities are found in the pre-frontal regions, the anterior cingulate cortex, portions of the basal ganglia and the limbic system. These aspects are in accordance with neuropsychological data that show significant impairments in memory, verbal fluency, visual confrontation naming, and set-shifting [105].

Apathy and Parkinson’s disease
The apathy in PD has a high prevalence of up to 70% [106]. Over the past 10 years, a series of studies on apathy in PD and in other neurodegenerative diseases showed the depiction of diagnostic criteria created by a task force, including members of the Association Française de Psychiatrie Biologique, the European Psychiatric Association, the European Alzheimer's Disease Consortium and experts from Europe, Australia and North America.

The initial studies of Marin defined apathy as a set of behavioral, emotional, and cognitive features including a reduced interest and participation in the main activities of daily life, a lack of initiative, a trend towards early withdrawal from social activities and indifference [107]. From the behavioral point of view, the apathy is characterized by a lack of effort and productivity and behavior of dependence on others. From the cognitive point of view it is characterized by loss of interest; while on the emotional side, it presents a lack of concern for difficulty and a reduced response to both negative and positive events [107]. These early observations outline the following guidelines for the definition of apathy:
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• diminished motivation, the core feature of apathy, must be present for at least 4 weeks;
• the impairment has to be found in at least two among the three dimensions of apathy (i.e. reduced goal-directed behavior, goal-directed cognitive activity and emotions);
• there should be identifiable functional impairments attributable to apathy.

Apathy diagnosis should furthermore exclude all cases where symptoms and conditions mimicking apathy are found [89].

Although these criteria are well defined, there are symptoms overlapping between apathy and depression such as anhedonia (inability to feel pleasure) [108], which led many researchers to consider apathy as a subcomponent of the depression; today this aspect is still considered. However, a recent study showed that the apathy and the depression are separate disorders in PD [109]: 161 patients with PD were subjected to the administration of the Beck Depression Inventory-II (BDI-II) scale and the Apathy Scale (AS), both considered valid and reliable for the evaluation of depressive and apathetic symptoms, and the results indicated that 17% of the subjects had only apathy without depression, 9% only depression and 16% both apathy and depression.

This allows us to consider apathy and depression as independent syndromes with different symptoms. Depression would be characterized by low mood, feelings of worthlessness, perception of failure (for the past and the future) while apathetic subjects would show lack of interest and no reaction to positive and negative events of life.

According to Varanese et al [110], the impaired implementation of novel cognitive strategies has a pivotal role in the inefficient storing and recalling of new information as well as in abstract reasoning and problem solving. They proposed therefore that this altered mechanism is the underpinning of apathy. The patients (with and without apathy) were subjected to the Apathy Scale, the Hamilton Depression Rating Scale and a neuropsychological battery for executive functions, attention, speed information, processing and learning, long-term memory (recall and recognition) and working memory [110]. The two groups, which did not differ in age, education and history of illness, had different scores (worse for apathetic patients) in tests of memory (recall) and in executive functions (Wisconsin Card Sorting Test - WCST). Since these tests require the use of strategies of categorization, planning and research of new criteria, they are considered sensitive to prefrontal and/or basal ganglia damage, which disrupt the associative pathways to the prefrontal cortex. In summary, the authors concluded that apathy should be considered as an early manifestation of the dysexecutive syndrome in PD [110].

The neurobiological substrates of apathy are unknown, but it has been hypothesized that it involves the anterior cingulate cortex circuits and the dopaminergic pathways [111], specifically, the striato-thalamo-cortical circuit originating in the ventral tegmental area and ending in the anterior cingulate cortex through ventral striatum, ventral pallidum, medial dorsal thalamus. These limbic structures are involved in motivation and drive, and are important in translating motivation into action.

Conclusion

PD is an insidious and multifaceted disease. As the above reported data clearly demonstrate, its motor symptoms may only represent the tip of a massive iceberg while the hidden part, that may have the biggest impact on daily life of patients and family members, consists of behavioural, cognitive and emotional symptoms. Some of these manifestations are intrinsic to PD, and some are the complications of therapies used for motor manifestations. Hence, to achieve a better management of the disease, it is important to know all these aspects and the impact of therapies on its global course. An early diagnosis of both motor and non-motor symptoms could be achieved by a teamwork of skilled professionals including neurologists, neuropsychologist and neuroradiologists. Behavioral and mood disturbances, cognitive and emotional dysfunctions should be carefully assessed and treated; pharmacological and non pharmacological interventions should be planned and employed. A multidimensional approach is strongly recommended.

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