Clinical and Experimental Neurosciences and Psychiatry
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PhD Thesis

Neuropsychiatric and cognitive symptoms in Parkinson's disease: the contribution to subtype classification, to differential diagnosis, their clinical and instrumental correlations

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Everything habitual draws around us an ever firmer net of spider-webs; and soon we notice that the threads have become cords and that we ourself are sitting in the middle as the spider who has caught himself and has to live on his own blood. That is why the free spirit hates all habituation and rules, everything enduring and definitive, that is why he sorrowfully again and again rends apart the net that surrounds him: even though he will as a consequence suffer numerous great and small wounds - for he has to rend those threads from himself, from his own body and soul.

F. Nietzsche

List of abbreviation

PD: Parkinson’s Disease

PSP: Progressive Sopranuclear Palsy

NMS: Non-motor symptoms

CI: cognitive impairment

NPS: neuropsychiatric symptoms

ICDs: Impulse Control Disorders

DAs: dopamine agonists

DRT: dopamine replacement therapy

PDD: Parkinson’s Disease Dementia

DLB: Dementia with Lewy bodies DLB

PIGD: postural instability gait disorder

PDQ-39: The Parkinson's Disease Questionnaire-39

MCI: Mild Cognitive Impairment

LBs: Lewy Bodies

UPDRS-III: Unified Parkinson’s Disease Rating Scale–Part III

H&Y: modified Hoehn and Yahr scale

PET: Positron emission tomography PET

SPECT: single photon emission computed tomography

MRI: magnetic resonance imaging

fMRI: functional magnetic resonance imaging

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1. Introduction

1.1 Non-motor symptoms of PD

A consistent body of epidemiological, pathological, and clinical evidence suggests that PD can no longer be considered as only a complex motor disorder characterized by extrapyramidal symptoms, but rather as a progressive multisystem disease—or more properly, multiorgan disease—with several motor and non-motor symptoms [1].

Indeed, in the last years it has been clear that person affected by PD experience a wide range and nature of non-motor symptoms from gastrointestinal to sleep disorders, from dysautonomia to cognitive problems, from apathy to depression either occurring in isolation as the dominant feature or in combination [2]. To make the all picture even more complex, growing evidence established that PD can be divided into a preclinical phase (supported by molecular or imaging markers), a premotor/prodromal phase (with non-motor symptoms) and the motor phase, the 'tip of the iceberg' [3] [Fig 1.1].

Therefore, while some non-motor symptoms dominate in the early or even in the 'premotor' phase of PD [4], others complicate the clinical picture throughout the disease (pain, fatigue) and especially in its advanced stages (dementia, apathy, dysautonomia), as shown in the Sydney multicenter study [5] report at 20 years. In addition, some NMS are related to drug therapy.

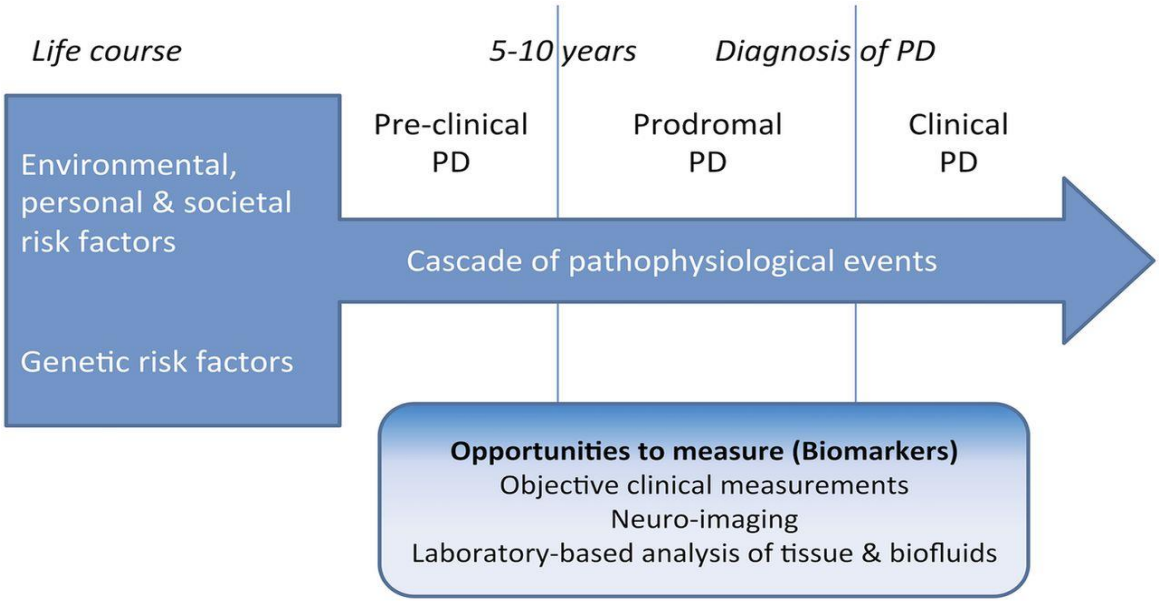

Fig 1.1 Adapted from The prediagnostic phase of Parkinson's disease. Noyce AJ, Lees AJ, Schrag AE. J Neurol Neurosurg Psychiatry. 2016. A schematic showing determinants of risk, the prediagnostic phase (preclinical and prodromal phases) and clinical phase of PD, along with the parallel application of risk and disease progression markers to measure disease activity across phases.

1.1.1 Pathogenesis of NMS

The traditional concept that the first neuropathological insult leading to PD is the degeneration of neuromelanin-containing neurones in the pars compacta of the substantia nigra (resulting in depleted levels of the dopamine) has been challenged. Many studies, spearheaded by the Braak theory [6, 7], suggest that a non-dopaminergic process is key to the non-motor symptoms of PD, many of which start well before the motor Parkinson's features emerge, and give clear evidence of differential neuronal degeneration involving several neuropeptide pathways in the brain in PD [8].

The well-known theory of Braak [6, 7] indicates that the pathological landmark of PD, the

Lewy bodies, can be identified in several neuronal populations other than the dopaminergic mesencephalic ones [9]. Following the ascending gradient of neuronal involvement throughout disease progression, six neuropathological stages of PD have been identified [7] [Fig. 1.2].

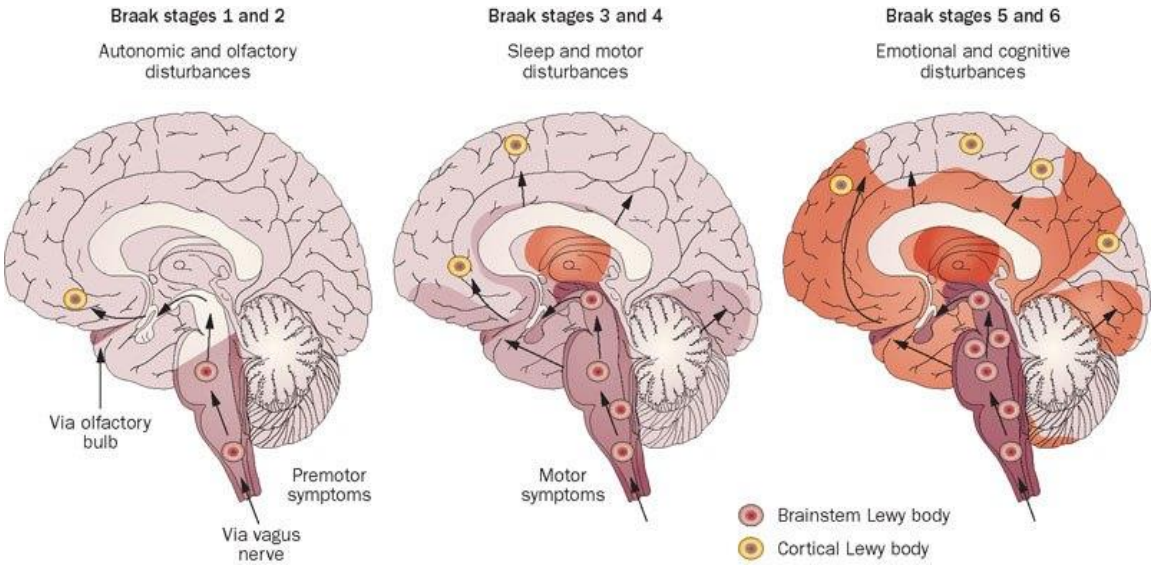

Fig 1.2. The Braak stages of PD. Adapted from:: Doty RL (2012) Nature Reviews Neurology 8, 329-339.

In stages 1 and 2, defined as “presymptomatic stages”, the Lewy bodies are confined to the anterior olfactory nucleus, olfactory bulb, dorsal motor nucleus of the glossopharyngeal and vagal nerves, locus coeruleus, and reticular formation. In stages 3 and 4 (“intermediate stages”), the neuropathological damage extends to the substantia nigra pars compacta, other mesencephalic nuclei, the prosencephalon and meso-allocortical regions; during these stages, the motor symptoms develop and progressively

worsen. Eventually, in stages 5 and 6 (“advanced stage” of PD), neocortical, prefrontal, and associative cortices are pathologically involved; in these latter stages, severe motor disturbances are accompanied by cognitive and behavioral symptoms.

Despite Braak staging does not provide an overall explanation for all NMS and premotor findings, it is still helpful in understanding the pathogenesis of NMS when combined with a broader view of PD as being more than merely a disorder of dopamine deficiency in the brain [10]. Indeed, clinically, NMS comprise a range of clinical signs and symptoms resulting from multiple neurotransmitter deficiencies and differential rates of neurodegeneration within the central and peripheral nervous systems as well as the gut from the colon-rectum to the salivary glands [2, 11-13] [fig 1.3]. Nevertheless, the clinical diagnosis of PD rests on the identification of the characteristics related to dopamine deficiency that are a consequence of degeneration of the substantia nigra pars compacta.

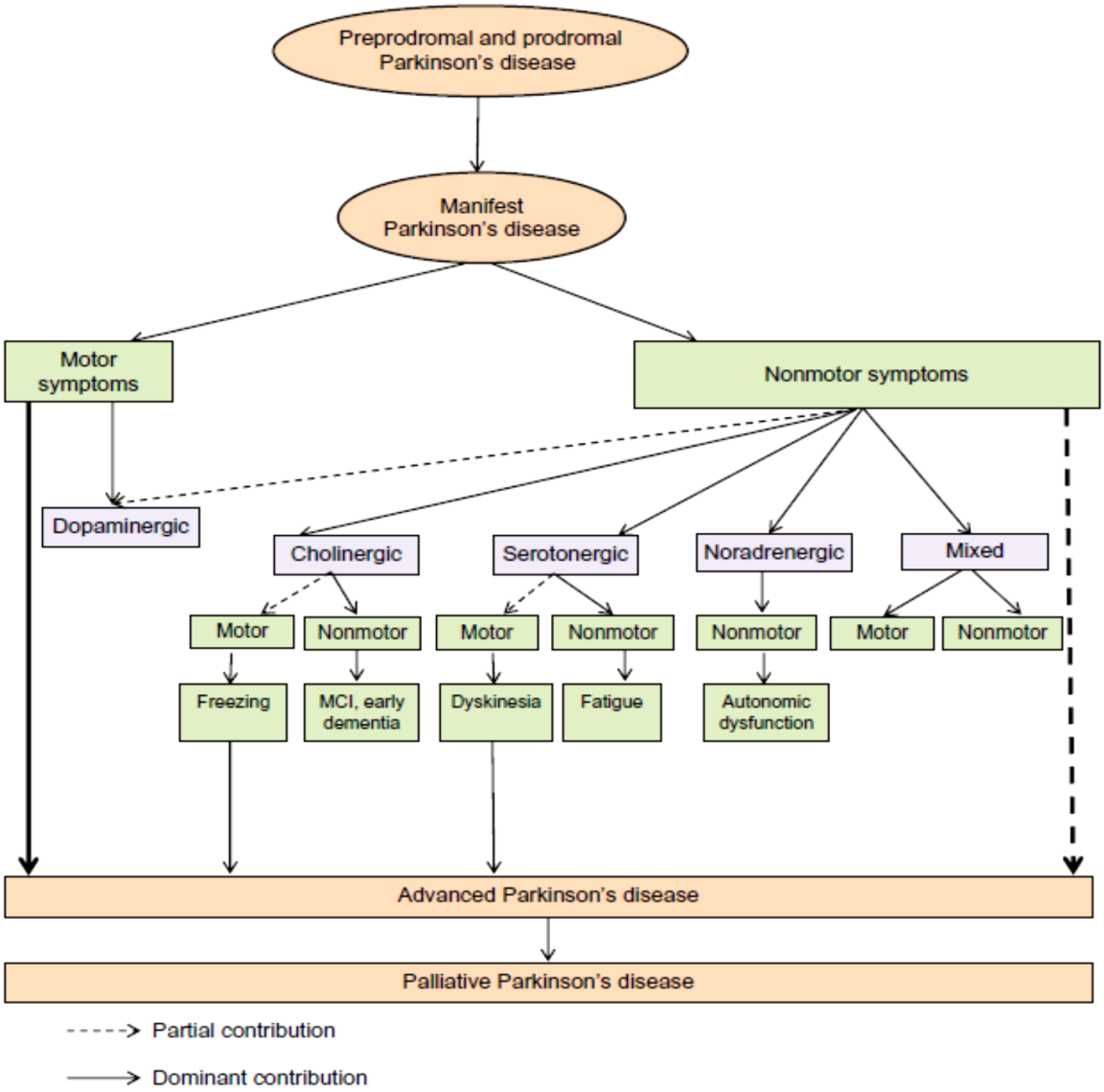

Fig 1.3. Adapted from: Nonmotor Subtyping in Parkinson's Disease Anna Sauerbier, Miguel Rosa-Grilo, Mubasher A. Qamar, K Ray Chaudhuri. Int Rev Neurobiol. 2017;133:447-478 1.1.2 The breadth of the issue: the impact of NMS

NMS are prevalent in over 90% of people with PD from untreated stage to advanced [14-18]. As the average age and life expectancy of the population increases, and given that PD is the second most common neurodegenerative disorder, the non-motor features of PD become increasingly important [19, 20]. Indeed, despite the emphasis on motor

symptomatology, several studies have shown that the non-motor symptoms of PD, such as depression, psychosis, falls, and sleep disturbance, have greater significance when assessed by quality-of-life measures, institutionalization rates, or health economics [21-28]. “The Sydney Multicenter Study of Parkinson’s Disease”, a prospective study of patients with PD followed up for 15–18 years, describes the role and effect of the NMS complex during the disease course and shows that non-levodopa responsive non-motor symptoms are the most disabling feature of the disease [20]. In particular, the major causes of disability in patients surviving for 15 or more years were falls, autonomic disturbance, neuropsychiatric symptoms, and dementia, aspects of the disease that are not improved by L-dopa. Falls occurred in 81% of patients, and 23% sustained fractures. Cognitive decline was present in 84%, and 48% fulfill the criteria for dementia. Hallucinations and depression were experienced by 50%. Choking has occurred in 50%, symptomatic postural hypotension in 35%, and urinary incontinence in 41% [20]. Accordingly, the PRIAMO study [29] found that nearly all patients with PD reported at least one NMS, with fatigue and anxiety being the most frequent. In particular, the psychiatric symptoms were the most frequently reported (66.8% of the sample), followed by sleep (64.1%), gastrointestinal and pain (61.0%), fatigue (58.1%), urinary (57.3%), and attention/memory (44.7%). Moreover, they reported that apathy was the symptom associated with worse PDQ-39 score but also presence of fatigue, attention/memory, and psychiatric symptoms had a negative impact on quality of life.

In a survey by the leading UK Parkinson's charity, Parkinson's UK, members rated

symptoms such as sleep disturbance, pain, constipation, urinary problems and dizziness to be as debilitating as and possibly more intrusive than their motor symptoms [30, 31].

This evidence demonstrates that NMS have a greater impact on health-related quality of life than do motor abnormalities, even early in the course of PD. Other studies have documented that NMS, specifically hallucinations, are the strongest predictor of nursing home placement for persons with PD. In the nursing home setting, NMS appear to be virtually universally present in patients with PD; individuals typically display multiple types of NMS, which occur with great frequency [32]. In persons with PD living at home, NMS in the form of neuropsychiatric symptoms also are important determinants of caregiver burden.

PD decreases quality of life for patients and imposes a significant economic burden on society comparable with other chronic diseases, such as congestive heart failure, diabetes, and stroke [33, 34]. A UK based cost analysis estimated that an annual direct cost of £4189 per year for PD managed at home rises to £19 338 for full-time institutionalization [26].

Although the importance and impact of NMS, they are often no recorder in clinical consultations. An international survey in 2010 showed that in up to 62% of cases, NMS of PD such as apathy, pain, sexual difficulties, bowel incontinence, and sleep disorders might remain undeclared to the health care professionals because the patients are either embarrassed or unaware that the symptoms are linked to PD [35].

In light of the importance and impact that NMS hold for persons with PD and for their family, it is vitally important that physicians caring for them are familiar with and are

attentive to diagnosing NMS when they occur.

With this in mind, NMS have now been incorporated in the new published diagnostic criteria for PD and in particular prodromal Parkinson's [36, 37].

1.2 Overview of neuropsychiatric symptoms in PD

NPS and cognitive symptoms occur in nearly all PD patients and may surpass motor symptoms in their impact on quality of life. NPS are identified to be integral to PD throughout the course of the disease, often developing in the early, untreated stages, before the onset of classical motor symptoms of PD [38-42]. Indeed, mood symptoms such as apathy, depression, and anxiety are common in PD and may precede the onset of motor symptoms by many years [4, 43, 44]. The concept of mood symptoms as a pre-motor stage of PD is consistent with the neuroanatomical staging system proposed by Braak and colleagues, who demonstrated early accumulation of alpha-synuclein within brainstem structures, followed by rostral spread into the midbrain, basal ganglia, and, eventually, the cortex [6, 45]. Following this pattern, dysfunction within the dorsal raphe nucleus and locus coeruleus may disrupt serotonergic and noradrenergic systems and may occur before significant loss of dopaminergic cells within the substantia nigra results in overt motor symptoms [46, 47]. Dysfunction in the dopaminergic system also contributes to the development of mood symptoms in PD, and the symptoms may vary both with the chronic dysfunction of the system and with fluctuating serum levels of levodopa or dopamine agonists [48].

In contrast, other neuropsychiatric symptoms such as cognitive dysfunction, dementia, and psychosis are more common in later stages of the disease and with the effect of DRT. Particularly dopamine agonists that cause hyperdopaminergic states, has been associated with psychosis, ICDs, excessive daytime sleepiness, and hallucinations.

1.2.1 Depression

Depression is the most common mood disorder in PD and is more common than in age-matched controls in other chronic diseases, such as diabetes, hypertension, coronary artery disease, or congestive heart failure [44, 49-52]. The estimated prevalence of depression varies widely between studies, and depressive symptoms have been reported in up to 90 % of patients [51]. Due to the broad spectrum of depressive symptoms, the types of depressive disorder considered in the studies influence the prevalence.

A systematic review in 2015 estimated that 50–70 % of patients with PD had been affected by symptoms of depression [53], while others report that 35 % had clinically significant depressive symptoms and 17% met criteria for major depressive disorder. Depression in PD typically shows an elevated degree of dysphoria and irritability, pessimism about future, with low levels of inadequacy and sense of guilt [54].

A significant biological rather than a pure reactive basis for depression associated with PD is probable and could, in part, be the result of damage to serotoninergic neurotransmission as well as limbic noradrenergic and dopaminergic mechanisms [2]. Studies have suggested that symptoms of depression may precede the diagnosis of PD

from 5 up to 20 years [4, 2, 41, 43, 55] years and that depression is associated with an increased risk of developing clinical PD with an incidence of 23% [56].

Notably, some patients experience symptoms of depression that emerge or worsen during off periods, when serum (and presumably brain) levels of dopaminergic medication are lower and the parkinsonian motor features are inadequately treated [47].

1.2.2 Anxiety

Anxiety is the second most common affective disorder in PD, with an estimated 40–50 % of patients experiencing clinically significant symptoms of anxiety, and approximately one third of patients meeting diagnostic criteria for anxiety disorder [57-59]. Anxiety disorders can also be a preclinical risk factor [41, 60]. Anxiety syndromes in PD include generalized anxiety, social phobias, specific phobias (including fear of *off* periods or freezing), and panic attacks; the symptoms are frequently co-morbid with depression [57-59]. Anxiety symptoms may be present throughout the day but are frequently encountered during *off* periods of insufficient motor control, or during the transition from *on* to *off* periods. Similar to depression, it is essential to screen for anxiety symptoms that vary with motor symptoms, and to adjust dopaminergic medications to limit or prevent off periods and motor fluctuations.

1.2.3 Apathy

Apathy, defined as a lack of feeling, emotion, interest, concern and reduced energy, has

now been established as a distinctive symptom of PD independent of depression, somnolence, and fatigue [61, 62]. Indeed, apathy ranges from 17 to 70 % of PD patients [61-65] and affects 20– 40 % of PD patients without dementia, and up to 60 % of patients with PD and dementia after 5–10 years [66-68]. Further, studies reported on prevalence of apathy in treatment-naïve PD patients [38, 69, 70].

Patients with PD have higher levels of apathy than do equally disabled patients with osteoarthritis, which indicates a neurodegenerative contribution [71]. Negative symptoms such as apathy, anhedonia, and fatigue could be due to neuronal degeneration in areas that mediate goal directed behavior (i.e., frontal-subcortical areas) or reward centres (i.e., dopaminergic projections between the ventral tegmentum and nucleus accumbens) [72, 73]. The features of apathy in the disease respond only slightly to dopaminergic drugs, possibly indicating more extensive contributions from other neurotransmitter pathways.

Apathy shares many symptoms with depression, including loss of interest in goal-directed behaviors and emotional blunting, but is differentiated by the relative absence of mood symptoms. Apathy is also correlated with worsening cognitive impairment, is a predictor of further cognitive decline and dementia [74, 75] and it is a major cause of caregiver distress [76].

1.2.4 Anhedonia

Anhedonia, defined as “the inability to experience pleasure” from activities usually found enjoyable on bases of subjective emotional experience for positive and negative events

[77, 78], is a key symptom of depression and of apathy in PD patients. In this definition, the focus is on the subjective emotional experience of the patient and not on interpersonal behavioral aspects. Anhedonia is generally seen as a symptom and not a syndrome [79]. As a symptom, it may be part of the syndrome of apathy, following the criteria of Marin and their subsequent revisions [81-82]. It is also considered part of major depressive disorder, and of the negative syndrome of schizophrenia [83]. The prevalence of anhedonia in PD patients varies from 10 to 40% [84, 85]. The association between anhedonia, apathy, and depression is intricate because the diagnostic criteria are unclear and there are overlaps of symptoms between these neuropsychiatric disorders. Several studies highlighted a correlation between anhedonia and depression, proving that PD patients with depression showed higher levels of anhedonia than PD patients not depressed [85-87]. Lemke et al., [86] reported that the frequency of anhedonia in PD (N=657) ranged about the 45,7% of all sample and the 79,7% of depressed subjects. In contrast, other authors [88] showed no significant correlation among anhedonia, depression and apathy. The impact of anhedonia on motor symptoms and quality of life has hardly been studied.

1.2.5 Alexithymia

Alexithymia, mainly defined as the inability to symbolize or mentalize emotions [89], is a fairly common phenomenon in PD (ranged from 18 to 23.8%) and it seems related to the severity of depression symptoms in PD patients [90]. Particularly, Costa et al., [91]

reported that alexithymia was significantly more severe in patients with major depressive disorder (MDD) than in patients with minor depressive disorder (MIND) and without depression (NODEP). Assogna et al. [92] reported an alexithymia prevalence rate of about 50% in PD patients with MDD and 25% in patients with MIND. However, previous studies [93, 94] proposed that depression symptomatology does not predict and does not completely explain the presence of alexithymia in PD, suggesting that depression and alexithymia may be partially overlapping but independent affective disorders [89, 95].

In a small controlled study, Poletti et al. estimated [93] that 23.8% of the *de novo* PD patients are alexithymic, 26.2% borderline alexithymic, and 50% non-alexithymic. These percentages were not statistically different compared with controls. On the other hand, they observed that *de novo* PD with the postural instability gait difficulty motor subtype presented more alexithymic features than PD patients with tremor-dominant phenotype, suggesting that the postural instability gait difficulty subtype could represent a risk factor for developing alexithymia [95].

1.2.6 Psychosis

Psychosis affects more than 50 % of patients with PD at some time, and may affect up to 75%of patients with PDD [20,97,98]. Psychotic symptoms are frequently caused or worsened by anticholinergic or dopaminergic treatment, particularly with dopamine agonists, but also occur in untreated PD [98, 99]. The results of the PRIAMO study [100], assessing psychosis in early PD patients (H&Y score ≤ 2, disease's duration (median) 3.4

years), reported that the prevalence of psychotic type symptoms at baseline was 3%; the incidences at 12 and 24 months were 5.2% and 7.7%, respectively. The development of psychosis over the 24-month period was associated with longer disease duration and prescription of dopamine agonists at baseline.

Psychotic symptoms in PD have been related to Lewy body pathology affecting the temporal lobes and causing diffuse cortical cholinergic dysfunction, and to serotonergic dysfunction with increased serotonin-2A (5HT2A) receptor binding potential in multiple areas including visual processing areas and prefrontal cortex [101]. Although visual hallucinations are commonly viewed as a side effect of treatment for PD, neuronal degeneration of the pedunculo pontine nucleus, locus coeruleus, and the dopaminergic raphe nuclei might be causative [102].

Symptoms range from mild visual distortions and the sense of *presence* to fully formed, complex hallucinations. Visual images of people or animals are the most common type of hallucination, although other sensory modalities may also be affected. Auditory hallucinations have been reported in 8%of patients with PD psychosis, but predominant auditory symptoms such as those seen in schizophrenia are uncommon [103]. Grandiose, religious, and/or persecutory hallucinations are also rare in PD psychosis. PD psychosis is also distinct from delirium, as the psychotic symptoms occur without significant change in baseline cognition. Delirium can occur in advanced dementia or can be induced by concurrent infection or dopaminergic drugs. Sudden drug withdrawal can precipitate a parkinsonism hyperpyrexia or neuroleptic malignant syndrome, which may be associated

with delirium [104]. Delusions are less common in PD and affect a subset of 5 30 % patients [20, 96], but these fixed beliefs are often refractory to treatment. Psychotic symptoms strongly correlate with the need for decline in cognitive performances, nursing home placement and with mortality [105].

1.2.7 Impulse Control Disorders

ICDs include pathologic gambling, compulsive buying, hyper-sexual behavior, and binge eating [106]. Hobbyism, a compulsive over-interest in other activities such as collecting items or following sports scores, may also occur. These behaviors vary widely in severity but can have devastating financial and social consequences for patients and families. ICDs occur most frequently in patients using DAs, although they are also reported in patients using levodopa [107]. A cross-sectional study of 3090 patients with PD found that 17 % of patients using a DA demonstrated an ICD during 6 months of treatment, versus 7 % of patients not on a DA [107]. Longitudinal studies have found even higher prevalence, with nearly 40%of patients receiving DA therapy developing an ICD during 4 years of treatment [108, 109]. The risk for developing ICD appears to increase with higher doses of dopaminergic medications, although they can occur even at low doses. Other risk factors include younger age, male sex, cigarette smoking, history of substance abuse, and history of impulsive behaviors [106, 110]. The oral DAs pramipexole and ropinirole appear to impart similar risks for developing ICD, and it is unclear whether the use of extended release oral formulations decreases these risks. In contrast, a cross-sectional study of

patients using oral DA versus transdermal rotigotine did find a significant reduction in ICD with rotigotine, with 42 % of patients on oral pramipexole or ropinirole meeting criteria for ICD based on the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease Rating Scale (QUIP-RS), versus 19 % of patients on transdermal rotigotine [111]. Adjunctive use of rasagiline was also associated with an increased risk for ICD in this study, as well as in isolated case reports [112].

1.2.8 Cognitive Dysfunctions and Dementia in PD

The neuropsychological deficits in PD range from mild executive dysfunction in the early stages to MCI and dementia in the later stages (Table 1.1). Cognitive impairment is common, with up to 50 % of PD patients showing deficiencies in one or more cognitive areas within 5 years of diagnosis [113]. In newly diagnosed untreated patients with PD, cognitive impairment ranges from 18% to 36% of incident cohorts [38]. Affected domains include psychomotor speed, memory, executive function, visuospatial skills, and attention, while language appears to be less affected. Cognitive deficits have also been divided into frontal and posterior types. It has been proposed that deficits reflecting cognitive dysfunction in more posterior parts of the brain such as semantic fluency or visuospatial deficits carry a worse cognitive prognosis [114].

Table 1.1. Cognitive deficits and example of tests used in diagnosis

Cognitive Domain	Description of cognitive deficit	Examples of neuropsychological tests
Executive Functions	↓↓ verbal fluency, ↓ set-shifting, planning & concept formation; may influence memory functions	Verbal fluency (semantic & phonemic); ToL/SoC (CANTAB); WCST; Stroop
Visuospatial & constructural function	Globally impaired visual perception (predisposes to VH); impaired size and form discrimination; ↓ face recognition; marked impairment on clock-drawing test	Clock-drawing test; Benton's judgement of line orientation
Memory	Episodic memory less affected than AD; ↓ visual & verbal memory; recall > recognition affected early on	Free and cued recall, e.g. CVLT or RAVLT
Attention & Working Memory	Fluctuating alertness; auditory and visual attentional deficits	Digit span; Trail Making Test
Language	Less impairment than AD; less affected until severe disease	Boston naming test

ToL Tower of London test; SoC Stocking of Cambridge (both from CANTAB [Cambridge Neuropsychological Test Automated Battery]); WCST Wisconsin Card Sorting Test; CVLT California Verbal Learning Test; RAVLT Rey's Auditory Verbal Learning Test; VH visual hallucinations

1.2.8.1 Executive functions

Executive function refers to a set of cognitive processes that control goal-directed behaviours from goal formulation and intention formation to successful execution and processing of the outcome [115]. Impairment of executive functions constitutes the core feature of neuropsychological dysfunction in PD patients and can be present from the early stages [116-118]. Executive dysfunction in PD is characterized by deficits in internal control of attention, set shifting, planning, inhibition, conflict resolution, impairment in dual task performance, and on a range of decision-making and social cognition tasks [115]. These impairments are similar, but not identical [119] to those seen in patients with

frontal lesions and are thought to represent a dysfunction of the fronto-striatal neuronal circuitry [120, 121].

Indeed**,** the dopaminergic neurons in the posterior putamen, which are severely affected in PD, are particularly relevant for the execution of automatic behaviours. It has been suggested that PD patients compensate by relying on non-routine action control mediated by the relatively preserved rostromedial striatum. Consequently, due to basal ganglia dysfunction, PD patients need to exert cortical executive control even for routine tasks, which healthy individuals perform automatically [115].

Executive deficits in PD are related to depression and apathy, postural instability, freezing of gate, and other gait problems [122-124].

Different executive functions are affected to different degrees and at different stages of PD. Attentional set shifting is compromised earlier than planning, and the decline in spatial working-memory is faster or more severe than for other forms of working memory [115]. The predictors for a more pronounced decline are male gender, older age, and later onset of disease. The progressive executive and general cognitive decline in PD reflects the increasing involvement of other non-dopaminergic neurotransmitter systems such as the cholinergic system [125].

1.2.8.2 Visuospatial abilities

Visuospatial impairment has been described in patients with PD [126, 127], even when tests reveal few motor component involvement [128]. In non-demented patients with

mild to moderate PD visual impairment has been found to correlate with impairments in cognition (i.e. executive functions and verbal memory), postural control and gait, and functional disability [129]. Furthermore, visuospatial impairment was found to be more severe in patients with PD and dementia (PDD) than in AD patients with an equivalent severity of dementia [130-133]. It has been suggested that such visuospatial impairment may be at least partly attributable to frontal-executive dysfunction in addition to deficit in temporal and parietal cortices.

1.2.8.3 Memory

Memory impairment has frequently been reported in PD and is characterized by poor free recall and relatively better recognition. Impaired immediate and delayed recall can largely be remedied by semantic cueing or probing [117,134] suggesting that the memory deficits in PD may be due to retrieval problems [135-137], as opposed to the deficient encoding seen in Alzheimer Disease [138-140]. This may reflect a deficiency in internally-cued search strategies due to the dysexecutive syndrome [141]. However although a frontal-type memory impairment is the most common memory profile in PD, impairment of both recall and recognition, a pattern similar to that found in AD [142] has been found. This finding suggests that hippocampal pathology [143, 144] may also contribute to memory impairment in a subgroup of patients with PD.

1.2.8.4 Attention

Attentional dysfunction is prominent among the cognitive impairments described in PD and is probably closely related to the executive function impairment reported in these patients. This hypothesis is supported by several studies showing that attentional dysfunction appears most usually in connection to complex tasks requiring shifting and/or sustained attention [145, 146], as well as mental calculations that require sustained mental tracking [147]. Attentional dysfunction is a characteristic feature of PDD and DLB, and consists both of reduced and fluctuating performance [148]. The underlying pathological substrate of this dysfunction seems to underlie on metabolic activity [149] and cholinergic deficits in the thalamus [150].

1.2.8.5 Mild Cognitive Impairment and Dementia

A task force of the Movement Disorder Society (MDS) [151] has recently outlined the diagnostic criteria for MCI in PD.

Single-domain PD-MCI was initially divided into amnestic and nonamnestic subtypes. More recently, single-domain PD-MCI has been subdivided based on the cognitive domain impaired without preferential reference to amnestic deficits [152]. Executive deficits are particularly common in single-domain PD-MCI [152], justifying the departure from the amnestic/nonamnestic distinction that had been borrowed from experience with MCI in the general population.

MCI can include executive dysfunction and impairment of attention and working memory,

as well as deficits confined to language, memory, or visuospatial domains. MCI is a predictor of dementia in PD, which in the long term develops in up to 80% of patients [5, 137, 153]. Indeed, most patients who develop PD-MCI will progress to dementia within 5 years [154], and over 80% of patients surviving 20 years after diagnosis of PD will have dementia [5].

An MDS task force [155] has also outlined the diagnostic criteria for dementia in PD. Impairment of executive functions, particularly word fluency, has been found to be a predictor of later development of dementia [156-158]. Dementia occurs in up to 40% of people with PD, a rate about six-times higher than that in healthy individuals [159]. Dementia is progressive and is clinically characterized by a dysexecutive syndrome with impairment of visuospatial abilities and memory on a background of loss of response to dopaminergic drugs including levodopa [160, 161]. Degeneration of nigral cells is implicated, and although presence of cortical and subcortical Lewy bodies is also likely to be causative, this link is controversial [162, 163]. Cholinergic cell loss in the nucleus basalis of Meynert is prominent in PD and forms the basis of cholinergic treatment for dementia in the disease. Patients with PDD exhibit greater cortical cholinergic deficits than those with Alzheimer's dementia (AD) [164].

The contribution of comorbid Alzheimer's disease and vascular pathology, as well as a possible genetic association with the APOE genotype, have also been implicated. Hippocampal volume, as detected by volumetric MRI studies, is diminished in PD with dementia to a similar extent to that in Alzheimer's disease [165].

1.3 From One to the Many: redefining PD

The amount of new knowledge the research brought about in last years is of such a breadth to break through the boundaries among PD as currently defined. The possible collapse of those very boundaries urges then the medical community to forge new categories, to better explain and better heal PD. In recognition of the profound changes in our understanding of PD, the International Parkinson and Movement Disorders Society (MDS) commissioned a task force to consider a redefinition of PD [166].

PD is a remarkably variable condition and beyond the complexity of its clinical manifestations, there is also a wide heterogeneity at individual level. PD varies in clinical features, dominant symptoms, and rate of progression from case to case. This variability has prompted a number of studies investigating the existence of PD subtypes, which divide PD patients into groups based on clinical or demographic features [167].

Recently the National Institutes of Health established subtype identification as one of the top three clinical research priorities in PD [168]. Indeed, identification of distinct PD subtypes is of great priority to shed light on underlying pathophysiology, predict progression and develop more efficient personalized care approaches.

There is currently no clear way to define and divide subtypes in PD. Many different groupings or subtype classification systems have been proposed, which raises questions about which are most useful and their implications for future research. Furthermore, the progressive nature of PD makes it important to consider the possibility that subtypes may

differ with disease duration, and that the relationship of specific symptoms to subtypes of PD may be different across the course of the disease. Two main approaches to deriving subtype classifications have been used: empirical classifications based on clinical observation of the heterogeneity of PD and data-driven classifications with cluster analysis to identify subtypes in a hypothesis-free manner. Data-driven cluster analysis has the potential advantage of a hypothesis-free approach, allowing broader interrogation of the features and unbiased estimates of factor importance [166, 168-170].

The first approach classifies subgroups on a single factor and looks for differences between groups. Two commonly suggested subtypes are onset age and tremor dominance. Age subtyping is proposed because young patients have more robust L-dopa response, more motor complications, and fewer cognitive disturbances [171-173]. Tremor predominant subtypes are proposed because they may have better prognosis and fewer cognitive disturbances [171-173] Other studies suggest other potential subtype identifiers; for example, olfactory loss correlates with cognitive impairment [174], and RBD correlates with autonomic dysfunction and higher dementia risk [175, 176].

Few studies have examined the influence of side and type of motor signs at disease onset and the presence of nonmotor PD symptoms. Some results indicated that patients with right-sided, tremor-dominant symptoms showed relative sparing of cognitive function [177, 178]. Conversely, Viitanen et al, found no association between side and type of motor signs at disease onset and cognitive impairment [179]. Baumann and collegues [180] reported faster motor progression in patients with a right-sided onset. However,

data on on the association of specific motor and nonmotor manifestations are rather contradictory. In the future, it may also be possible to subdivide PD according to pathogenic mechanism (mitochondrial predominant, inflammatory predominant, and so on).

In the second approach, clusters have been defined based on age, motor features, and, possibly, a non-motor symptom cluster. These variables correlate with different mortality, progression, motor complications, dementia, and behavioral symptoms [171].

The etiological and physiological bases of this heterogeneity are, however, very poorly understood. The mechanism for subtype differences is unclear. Potential explanations include the variability in comorbid pathology (eg, subtle Alzheimer pathology interacting with synuclein in the cortex), the relative vulnerability of substantia nigra (if “mainly motor” patients have more vulnerable nigral neurons, then they may present earlier with pure motor symptoms), or perhaps even the variable propensity for synuclein pathology to spread from region to region [181].

Efforts to define subtypes of PD attempt to provide a framework for studying this heterogeneity.

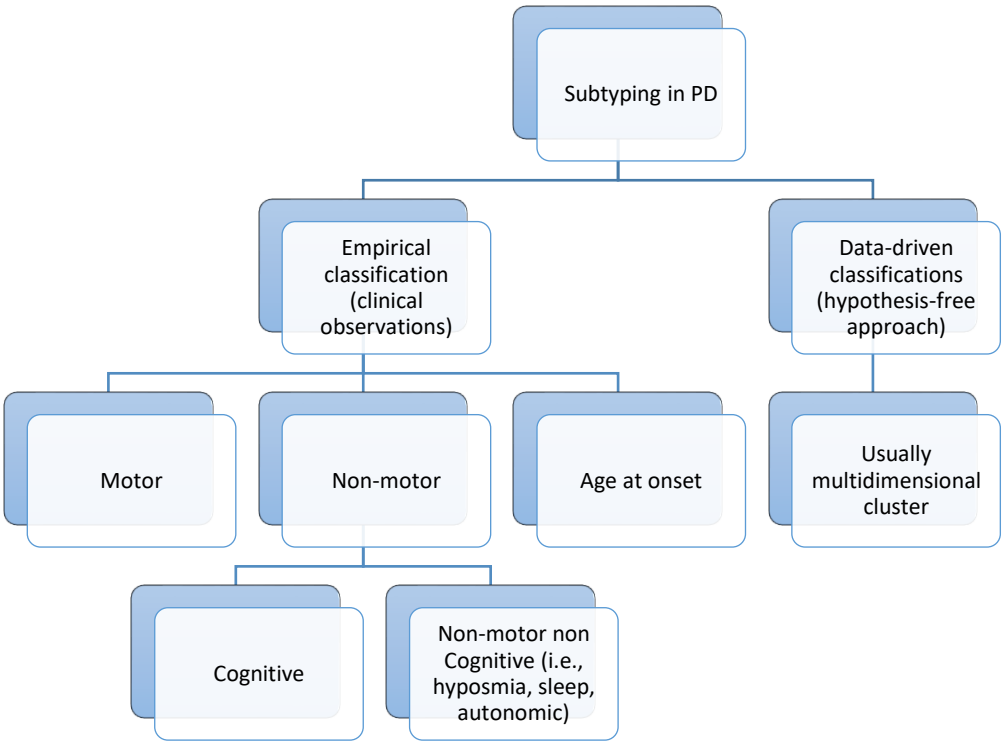

Fig 1.4. Approach to subtyping in PD. Adapted from Marras, C., & Chaudhuri, K. R. (2016). Nonmotor features of Parkinson's disease subtypes. Movement Disorders, 31(8), 1095–1102

1.3.1 Motor dominant subtypes of PD

The most commonly used empirically defined subtyping system divides patients into tremor-dominant or nontremor-dominant subtypes. Non tremor-dominant PD has been characterized as either akinetic-rigid or postural instability gait disorder (PIGD) phenotypes and sometimes a third, 'indeterminate' group [182]. Akinetic/rigid subtype overlaps with the previously known PIGD-dominant subtype [183] since it has been defined to describe a group of tremor-free patients with significant axial rigidity. Patients are easily classified in this system based on Unified Parkinson's Disease Rating Scale scores or MDS-UPDRS scores: PIGD and tremor scores can be calculated using their UPDRS-part

III items. Overall, it does seem that tremor-predominant subtype at onset has a more benign course of disease and slower progression that PIGD-dominant subtype [184]. Conversly, PIGD-dominant phenotype is associated with faster cognitive decline [185, 186], higher prevalence of depression and apathy [187], more hyposmia [188], higher prevalence of other NMS [189], and overall faster progression [182, 190]. Imaging and biomarkers studies corroborate such a difference between motor subtypes and provide a compelling reason to think that the subtypes are different in ways that link to etiology and pathophysiology. PET and SPECT studies indicated that severity of tremor is less related to measures of dopaminergic denervation than rigidity and bradykinesia [191]. The two subtypes differ on structural MRI parameters indicating that the non-tremor-dominant subtype of PD had higher gray matter atrophy in motor, cognitive, limbic and associative areas. Further, lower gray matter volumes in the presupplementary motor area and in the primary motor area were associated with greater severity of symptoms in patients with PIGD [192]. A study of functional connectivity with resting-state MRI raised the question on differences in underlying neural circuitry between subtypes showing that the PIGD score inversely correlated with subthalamic-putamen connectivity, whereas tremor score correlated with subthalamic-cerebellum connectivity [193].

Further support for the tremor-dominant/PIGD distinction comes from a functional MRI study [194] with a grip task in tremor-dominant and nontremor-dominant PD. Reduced activation in the prefrontal cortex and globus pallidus of patients with nontremor-dominant PD was found, suggesting differences in brain activation patterns between the

subtypes that extend beyond the occurrence of the tremor itself.

The etiology of the tremor-dominant/PIGD phenotype distinctions remains obscure, however.

When data-driven cluster analyses are applied and some nonmotor features are included, there still often existed a relative prominence of motor features in subtype solutions. However, when nonmotor and motor variables are both put into the same statistical model, many nonmotor variables are stronger than motor variables in subtype definition [167].

1.3.2 Non-motor dominant subtypes of PD

As knowledge of non-dopaminergic and nonmotor features has advanced, studies have been increasingly incorporating nonmotor variables, with clear improvement in cluster quality. Several nonmotor features such as cognitive impairment, sleep disorders, autonomic dysfunction, and hallucinations have emerged not only as important determinants of subtypes but also as stronger elements than motor variables in subtype definition [181].

NMS subtype patterns reflect phenotypes driven largely by dominant limbic, brain stem, or cognitive involvement, even at a very early motor stage of PD [195].

On the other hand, these broad clinical phenotypes reflect the underpinning convergence of deficits in multiple transmitter systems and pathways, including the cholinergic,

noradrenergic, and serotonergic systems that occur in PD [1, 196], [Fig.1.5].

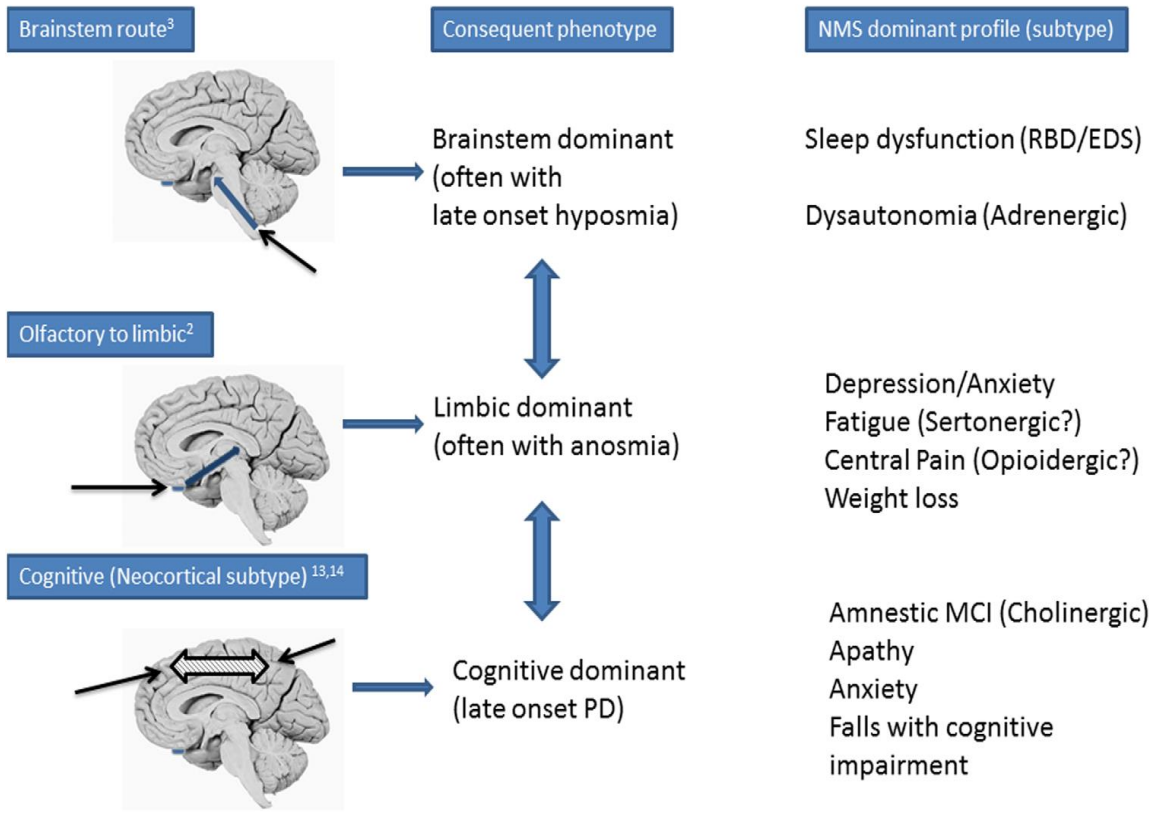

Fig 1.5. Possible routes of spread of pathology in PD as described from pathophysiological studies and consequent phenotypic expression and nonmotor subtypes. RBD, rapid eye movement behavior disorder; EDS, excessive daytime sleepiness; MCI, mild cognitive impairment. Hatched arrow in cognitive phenotype diagram indicates frontal and parietal involvement with underpinning cholinergic dysfunction. Figure adapted from Sauerbier et al. (Sauerbier A, Jenner P, Todorova A, Chaudhuri KR. Non motor subtypes and Parkinson's disease. Parkinsonism Relat Disord 2016;22(Suppl 1):S41-S46.

A proposal of seven different NMS dominant clinical phenotypes within PD mainly in early and untreated phase has been suggested based on clinical observation [196]. These observations have been based on three main routes of propagation of the pathology in PD. Based on areas of the brain dominantly involved in the pathway of the routes of

propagation, various subtypes are proposed. The phenotypic variants proposed are as follows [196]:

- park cognitive (predominantly presents with cognitive impairment at an early stage);
- park apathy (high scores on apathy scales);
- park depression/anxiety (early manifestation of these symptoms);
- park sleep (characterized by excessive daytime sleepiness or rapid eye movement behavior disorder);
- park pain (different pain syndromes dominate the clinical picture);
- park fatigue (exhibited as an independent and severe symptom);
- park autonomic (gastrointestinal, genitourinary symptom dominant, and adrenergic dysfunction dominant).

Park cognitive and Park apathy are likely related to the neocortical subtype, which shows pathology in the neocortex and the presupplementary motor (pre-SMA) in early PD. Park sleep and Park autonomic are underpinned by a brainstem spread of pathology in PD, while Park pain and Park fatigue are related to the olfactory to limbic route involvement [195].

However, these subtypes are not universally accepted.

In data-driven cluster analysis, NMS are often selected as predominant predictors of subtype description.

Erro et al. [197] performed a cluster analysis that incorporates the NMS-Quest and other

specific nonmotor specific symptom scales in a cohort of early, untreated patients with PD. They described two 'benign' clusters, one motor and one combining mild features of motor and nonmotor symptoms, and two more rapidly progressive clusters; one motor and one predominantly nonmotor. It suggests, as other cluster analyses have, that nonmotor symptoms are important defining features of PD subtypes.

Fereshtehnejad et al [181] recommended a cluster-derived subtyping in which three critical nonmotor features (MCI, RBD and orthostatic hypotension) identified the most rapidly progressive subtype at baseline. This was termed the diffuse malignant subtype [181]. The other two clusters in this study, mainly motor-slow progression and intermediate, showed more favorable course of progression, even though the diffuse malignant subtype had the same level of motor disability at baseline [181]. This study benefitted from a comprehensive list of motor and nonmotor features and longitudinal follow-up (>4 years).

The ONSET PD study [4], a prospective case-control study, analyzed 109 newly diagnosed drug-naive PD patients and 107 age- and gender-matched controls.

The results of cluster analysis identified four different subtypes. A first subtype was characterized by RBD-like and constipation cluster characterized by recurrent nightmares, dream-enacting behavior, and constipation. Second, a mood cluster characterized by anhedonia, apathy, and mood disturbances was identified. Third, a cognition-related cluster involving memory and attention problems, fatigue, and excessive daytime sleepiness (EDS); and fourth sensory symptom clusters dominated by pain and taste loss

were described. No cluster was associated with a specific motor phenotype or severity.

In a very recent study, Fereshtehnejad et al [198], proposed clinical criteria for subtyping PD. They applied a hierarchical cluster analysis on the Parkinson's Progression Markers Initiative (PPMI) dataset consisting of prospective longitudinal clinical characteristics, neuroimaging, biospecimen and genetic information of 421 de novo early PD patients. They aimed to develop criteria to assign patients to a PD subtype. They identified four composite domains: motor (UPDRS-II, UPDRS-III, and PIGD score), cognition (combining all available neuropsychological batteries in PPMI), RBD (RBDSQ score), and dysautonomia (SCOPA-AUT total score). They identified three clusters of PD subtypes. A "mild-predominant motor" cluster was characterized by patients with younger age, the mildest scores in motor UPDRS, sleep disorders, olfactory and autonomic dysfunction and the least affected cognitive performance in almost all domains at baseline. By contrast, the "diffuse malignant" cluster included patients with the worst scores in both motor and non-motor components (except for olfactory dysfunction and hallucinations). An "intermediate cluster" described an intermediate status in most motor and nonmotor manifestations at baseline. Interestingly, the authors were able to demonstrate that, despite similar disease duration, subtypes differed substantially in terms of neuroimaging, CSF biomarkers, clinical characteristics and disease progression over time. Indeed, patients with the diffuse malignant subtype have more prominent dopaminergic deficit on SPECT, more atrophy in PD-specific brain networks on MRI, a more Alzheimer's disease-like CSF profile and progress more rapidly on motor and cognitive performance [198].

NMS subtyping is an important step forward in the translation of pathophysiological advances in PD to clinical practice. Indeed, NMS subtyping would enrich the design of clinical trials and recruitment of patients as well improves the knowledge about the natural history of PD.

1.4 Unmet Needs and future directions

Such a broad clinical and pathophysiological heterogeneity poses a challenge to the clinicians and researchers. In particular, NMS represent “a challenge within a challenge” because they continue to be a key determinant of patients’ and careers’ quality of life at huge societal costs. NPS and cognitive symptoms contribute heavily to the burden of PD since the very early stage of the disease.

Further, the occurrence of NPS in PD patients may frequently be related to potentially additive mechanisms, including psychological reactions to disability, psychiatric symptoms caused by structural brain damage, and adverse effects of DRT. Indeed, knowledge is still limited about structural brain areas and the neuropathological and pathophysiological changes that may associate with NPS in PD. The main limitation of investigating these symptoms is that NPS are influenced by DRT and often are hardly differentiated from each other because of symptom overlaps.

The research in the field urges to fulfill crucial unmet needs, as highlighted also by the National Institute of Neurological Disorders and Stroke PD 2014 conference [168]:

- Extensive insight into untreated PD patients, who offer a suitable model to study the expression of NMS in comparison to motor symptoms and might also provide an unbiased framework to generate pathophysiological hypotheses able to explain the complex heterogeneity of PD.

- Major advances in understanding the diversity of NMS, their evolution in the diverse disease stages (untreated, early and advanced PD patients), and their differential effects on quality of life, as well as their possible progression pattern and their possible contribution in differential diagnosis with other degenerative parkinsonism.

- Identification of robust and replicable non-motor subtypes with the potential for prognostic indicators and specific treatments. Indeed, identifying different subtypes of PD is the mainstay for better understanding underlying disease mechanisms, predicting prognosis, and ultimately developing personalized management strategies.

- Collection of robust evidence for treatment of non-motor symptoms in PD.

- Implementations of technologies such as “body-worn” or “smart home” technologies that provide more detailed characterization of an individual’s motor, cognitive, and behavioral impairments for use in populations and settings.

- Identification of possible biomarkers suitable for defining the premotor stages of PD as well as the clinical patterns of PD into specific endophenotypes with a particular attention to biofluid biomarkers and biopsy of peripheral tissue that accumulates LBs (i.e., gut, salivary glands, and skin).
- Establishment of an integrated network of health-care specialist comprising PD nurse specialist, speech and language therapist, physiotherapist, occupational therapist, clinical psychologist and neuropsychiatrist in order to deal with the variegate symptoms occurring in PD such as dribbling of saliva, pain, sexual dysfunction, impulse control disorders and cognitive impairment.

Greater awareness of non-motor PD symptoms and successful answers to such a broad unmet needs have important practical implications for people with a chronic condition like PD. In particular, knowing the specific variability of each PD patient at baseline allows one to estimate prognosis and the spectrum of clinical manifestations that are likely to appear. This can be used to plan treatment protocol, avoid medications with high chance of side effects, guide clinicians as to what monitoring should be emphasized in specific patients and therefore more accurately counsel patients and families. Future clinical trials might also aim at investigating the effects of interventions on each PD subtype through subgroup analysis, to provide evidence for a tailored and more efficiently personalized treatment approach.

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2. Research Plan

The above-described scenario depicts several strands of research in the field of NMS of PD with specific emphasis on NPS and cognitive symptoms. The several unmet needs identified so far throw down the gauntlet to each researcher and clinician. The overarching aim of the work carried out during the Academic Years 2014-2017 was, therefore, to investigate the nature and relevance of NPS and cognitive symptoms in the diverse disease stages. To this end, their contribution in the characterization of different clinical phenotypes, in differential diagnosis, in disease complication, and their correlation with MRI findings have been evaluated in different scenario of untreated, early and advanced PD patients.

Given these premises, a research plan has been developed, the results of which will be discussed in the present dissertation:

- <u>NPS and cognitive symptoms in untreated PD patients:</u>
    - Identification of neuropsychiatric and cognitive symptoms differences according to the body side of onset of parkinsonism in unmedicated PD patients.
    - Identification of neuropsychiatric and cognitive symptoms differences according to the dominant motor subtype in unmedicated PD patients.
- <u>NPS and cognitive symptoms in early PD patients:</u>
    - The contribution of neuropsychiatric and cognitive symptoms in

differential diagnosis among PD and the major subtypes of PSP, the second more common degenerative parkinsonism.

  - Identification of affective impairment and emotional tone differences among PD and the major subtypes of PSP.

- <u>NPS and cognitive symptoms in advanced PD patients:</u>
  - Neuropsychiatric and cognitive characteristics of pathological gambling and not-otherwise-specified ICDs in PD patients
  - Investigation in MRI of morphometric correlates of ICDs in PD patients.
  - The contribution of NPS and cognitive symptoms in affecting the compliance to undergo MRI scan in PD patients

Finally, as overviewed in the “Ancillary Research” section, a parallel effort was made in identifying possible biomarkers on peripheral tissue (i.e., salivary glands) and, under the umbrella of two European Projects, in validation of NMS home monitoring tools and in defining an integrate platform based on dynamic and personalized orchestration of care services for PD patients.

3. General methodology: neuropsychiatric and cognitive batteries

Several neuropsychiatric and cognitive tests were applied in the research.

In this section, an overview of more commonly used tests and scales is given. In the following chapters, only the name/abbreviation of the tests and scales is specified.

3.1 Neuropsychiatric assessment

- The Beck Depression Inventory (BDI) [1]: 21-item self-report inventory. The total score is the sum of the individual item scores. We also calculated the psychic subscore and the somatic subscore by combining the first 14 items and the remaining 7 items, respectively.
- The Hamilton Depression Rating Scale (HDRS) [2]: 17-items scale for quantification of severity of depressive symptoms. The psychic subscore and the somatic subscore are also calculable.
- The Hamilton Anxiety Rating Scale (HARS) [3]: 14-items scale for quantification of severity of anxious symptoms.
- The 20-item Toronto Alexithymia Scale (TAS-20) [4, 5]: self- report instrument for the measurement of alexithymic characteristics. It comprises three subscales that assess distinct facets of alexithymia: F1, difficulty identifying feelings; F2, difficulty describing feelings; F3, an externally oriented analytic mode of thinking. To evaluate the prevalence of alexithymia, patients with a TAS-20 score greater than 60 were considered alexithymic, whereas patients ranging from 52 to 60 were

considered as borderline alexithymic and those scoring less than 52 were considered non alexithymic.

- The Snaith–Hamilton Pleasure Scale (SHAPS) [6]: 14 items self-rated instrument, used to evaluate hedonic tone. The subject is requested to agree or disagree with a statement in each item (definitely agree, agree, dis-agree, and definitely disagree). The four available answers are divided into dichotomous categories (agree=0; disagree=1), ranging from 0 to 14 and with a cut-off score of 2 as the best discrimination between "normal" (a score of 2 or less was categorized as hedonic) and "abnormal" (a score above 2 was categorized as anhedonic) level of hedonic tone.
- The Apathy Rating Scale (ARS) [7]: to assess apathetic symptom severity.
- The Parkinson's Psychosis Rating Scale (PPRS) [8]: to assess the severity of psychotic symptoms.
- The Structured Clinical Interview for DSM-IV TR (SCID-P) [9]: a structured psychiatric interview for the identification of psychiatric disorders according to the DSM-IV-TR criteria.

3.2 Cognitive assessment

- The Mini Mental State Examination (MMSE) [10]: a global index of cognitive impairment with the score ranging from 30 (no impairment) to 0 (maximum

impairment).

- The Rey's 15-word test – Immediate Recall (RIR) and Delayed Recall (RDR) [11]: to evaluate short- and long-term verbal memory, with total scores given by the total number of words recalled in each test.
- The Phonologic (PVF) and Semantic (SVF) Verbal Fluency tests [12]: to assess language ability: in which the total score is the total number of words produced during each test.
- The Copy of the Rey-Osterrieth picture (CRO) and Delayed Recall of the Rey-Osterrieth picture (DRO) [13]: to evaluate complex constructional praxis and long-term visual memory, with scores ranging from 0 (maximum impairment) to 36 (no impairment) on both tests.
- The Wisconsin Card Sorting Test – short form (WCST-SF) [14]: to explore executive functions. WCST-SF requires matching 48 cards to four key cards by color, shape, and number and choosing the six correct categories from feedback given by the examiner.
- Stroop Word-Color Test (SWCT) [15]: to assess frontal abilities of simple attention, attention shifting and control, which consists of three subtest: "word reading", "color naming" and "interference time".

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4. Untreated PD patients

4.1 Neuropsychiatric and cognitive symptoms and body side of onset of parkinsonism in unmedicated Parkinson's disease patients

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Hereunder we report an excerpt of the study. Full-text of the related article can be found at:

https://www.ncbi.nlm.nih.gov/pubmed/26173702

4.1.1 Background

Unilateral onset and asymmetric progression of motor symptoms are key clinical features of idiopathic PD [1].

Given the lateralization of several cognitive and affective functions in the cerebral hemispheres and the possible role of impaired dopaminergic transmission on non-motor symptoms in PD, the question raises whether body side of onset of parkinsonian motor symptoms might influence cognitive and/or neuropsychiatric domains in the early stages of PD. Indeed, a recent review of the published studies [2] concluded that PD patients with right-side motor symptom predominance (RPD) preferentially show difficulties in language and verbal memory, whereas those with left-side motor symptom predominance (LPD) have greater problems with tasks of spatial attention, visual-spatial orienting and memory, and mental imagery. More recently, however, Poletti et al. reported that the side of motor predominance scarcely influences cognition in the early, untreated stage of PD [3].

To further clarify the issue, in the present study we investigated the prevalence and severity of neuropsychiatric and cognitive alterations in a cohort of drug-naïve PD patients, divided into two groups according to the body side of onset of motor symptoms. We hypothesized the lack of relationships between motor lateralization and non-motor domains examined.

4.1.2 Methods

The study was carried out on 84 subjects diagnosed with PD according to the international guidelines [4], and 84 age-, sex- and educational level-matched healthy subjects (HC). PD patients were recruited during scheduled visits at the Outpatient Services for Movement Disorders of our Institutions. HC were recruited in the same geographical area. The study protocol was approved by the Ethical Committee of the "Fondazione Santa Lucia, IRCCS" and each subject signed an informed consent before enrollment. All subjects were right-handed and had vision and hearing sufficient for compliance with testing procedures. PD patients were all drug naïve of antiparkinsonian drugs. Six of PD patients were under therapy with antidepressant, 12 with benzodiazepine, none with antipsychotic drugs (Table 4.1).

Table 4.1: Demographic and Clinical Features of the Subjects Enrolled

	RPD (n=42) Mean ± SD	LPD (n=42) Mean ± SD	HC (n=84) Mean ± SD	F	df	P
Age (Years)	63.6±8	63±10.7	63.1±10.1	0.062	2	0.939
Education (Years)	11.4±4.7	11.5±4.7	11.9±3.9	0.165	2	0.848
Age at onset (Years)	62,4±8.2	61.8±10.7	Na	-	82	0.740
Disease duration (Years)	0.9±0.9	1.1±0.8	Na		82	0.451
H&Y score	1.6±0.5	1.5±0.5	Na	-	82	0.312
UPDRS-III score	15.1±8.9	15.1±8.3	Na	-	82	0.979
	n	**n**	**n**	**χ2**		**P**
Sex (F/M)	16/26	16/26	32/52	0.000	2	1
Minor depression (%)	13 (32%)	17 (39%)	7 (8%)	20.243	4	0.001*
Anxiety (%)	15 (35.7%)	16 (38%)	0 (0%)	0.051	1	0.821
Antidepressant drugs (%)	3 (7.1%)	3 (7.1%)	0 (0%)	0.000	1	1
Benzodiazepine (%)	5 (12%)	7 (16.7%)	0 (0%)	0.389	1	0.533
Antipsychotic drugs (%)	0 (0%)	0 (0%)	0 (0%)	-	-	-

SD=standard deviation; df=degrees of freedom; na=not applicable; H&Y=Hoehn and Yahr scale; UPDRS-III= Unified Parkinson's Disease Rating Scale – part III; *Statistically significant differences.

Common exclusion criteria for all subjects enrolled were:

1) major not stabilized medical illnesses;

2) known or suspected history of alcoholism, drug dependence or abuse, other neurological disorders, head trauma and mental disorders (apart from mood or anxiety disorders) according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition Text Revision (DSM-IV-TR);

3) Mini Mental State Examination (MMSE) score <26;

4) diagnosis of dementia according to the Movement Disorder Society clinical diagnostic criteria [5];

5) presence of vascular brain lesions, neoplasms and/or marked cortical and subcortical atrophy at CT and/or MRI scan.

PD patients were divided into 2 groups (42 LPD and 42 RPD) according to the body side of onset of motor symptoms. This was accomplished combining history data with the UPDRS part III scores in terms of laterality. At the time of assessment, in all patients parkinsonism predominated at the site of onset.

Neurological and Psychiatric Examinations

Demographic and neurological features were collected by trained neurologists at enrollment. Disease stage was measured by the modified H&Y scale, and the severity of motor symptoms by the UPDRS-III scale.

Within one week from enrollment, each subject was submitted to the SCID-P. Psychiatric diagnoses were made by a senior psychiatrist. In all PD patients, dopaminergic therapy was started following completion of the study protocol and carried out for at least 18 months to confirm the positive response to dopaminergic drugs.

Neuropsychiatric and Neuropsychological Evaluations

All participants underwent the following neuropsychiatric scales: HARS, HADRS, BDI (total, somatic- and psychic-subscores) and ARS.

The neuropsychological examination included: MMSE, RIR, RDR, PVF, SVF, CRO, DRO, WCST-SF and SWCT.

Psychopathologic and neuropsychological evaluations were performed by 2 trained neuropsychologists (FA and RL) who were blind to the study groups. Acceptable inter-rater reliability was defined as $k>0.80$.

Statistical Analysis

All analyses were performed using SPSS Statistics v22.0. Differences among the 3 groups were assessed by the chi-squared test for categorical variables and by a series of analyses of variance (ANOVAs) for continuous variables (i.e, demographic, neuropsychiatric and neuropsychological). Post-hoc comparisons were performed using Fisher's test for variables showing statistically significant differences on ANOVAs. A Student's t-test was performed for direct comparison of values measured for each variable between LPD and RPD patients. Further, we have compared the percentage of LPD and RPD patients varying 1.5 standard deviation (SD) from HC scores using the chi-squared test. For all tests, the level of significance was set at $p<0.05$.

4.1.3 Results

As shown in Table 4.1, there was no significant difference in any demographic feature among three groups. Moreover, there were no differences between RPD and LPD as to age at onset, disease duration or motor disability (Table 4.1).

Significantly higher prevalence of depression and anxiety and severity of neuropsychiatric impairment were observed in both LPD and RPD as compared to HC (Tables 4.1 and 4.2a).

There were no differences between LPD and RPD patients as to the prevalence or severity of neuropsychiatric disorders (Tables 4.1 and 4.2a). We have observed a trend towards significance at the BDI psychic, LPD subjects showing higher scores (Table 4.2a). Both RPD and LPD scored worse than HC at all neuropsychological tests except DRO, SWCT interference and WCST-SF categories scores (Table 4.2a). Again, there was no significant difference between LPD and RPD patients on any neuropsychological variables investigated (Table 4.2a).

In an ancillary analysis, we have calculated the percentage of LPD and RPD patients varying 1.5 SD from HC scores (Table 4.2b). These results revealed that higher percentage of LPD patients than RPD ones deviate from HC scores at HDRS, BDI total and BDI psychic.

Table 4.2a: Neuropsychological and Neuropsychiatric Scores

	RPD (n=42) Mean±SD	LPD **(n=42) Mean±SD**	HC (n=84) Mean±SD	F	df	P	Post Hoc analysis		
							P RPD vs. HC	**P LPD vs. HC**	**P RPD vs. LPD**
MMSE	28.4±2.1	28.7±1.8	29.1±1.3	2.350	2	0.0985	/	/	/
RIR	37.7±11.1	38.7±12.1	43.9±8.8	6.467	2	0.002*	0.0018*	0.0086*	0.658
RDR	7.6±3.8	8.4±3.8	9.5±2.8	4.548	2	0.0119*	0.0042*	0.0857	0.309
CRO	29.5±6	29.7±4.6	32±2.9	6.634	2	0.0017*	0.002*	0.005*	0.819
DRO	16.3±6.2	15.4±6.7	17.2±5.9	1.215	2	0.299	/	/	/
SWCT interference	43.8±19.2	41.8±13	39.1±12	1.557	2	0.213	/	/	/
SWCT word	16±5.8	15.9±5.2	13.9±3.4	4.267	2	0.0156*	0.0152*	0.0219*	0.905
SWCT color	22.1±7.6	20.6±5.6	16.2±4.3	3.725	2	0.0262*	0.0076*	0.207	0.215
SVF	19.3±6.3	19.7±5.4	22±5.5	4.361	2	0.0143*	0.0103*	0.0295*	0.730
PVF	31.1±11.8	32.1±12.1	37.1±11.1	4.880	2	0.0087*	0.0064*	0.022*	0.692
WCST-SF categories	5.4±1.4	5.5±1	5.8±0.6	2.544	2	0.0817	/	/	/
WCST-SF perseverative errors	2.5±4.0	2.5±3.2	1.1±2.5	4.292	2	0.0152*	0.0170*	0.0189*	0.972
WCST-SF non-perseverative errors	2.5±3.1	2.5±2.7	1.1±1.7	7.169	2	0.0010*	0.0023*	0.0023*	1
HARS	7.4±4.6	8.6±4.8	4.7±4	12.595	2	<0.0001*	0.0014*	<0.0001*	0.216
HDRS	7.4±4	8.5±4.5	3.5±3.7	26.024	2	<0.0001*	<0.0001*	<0.0001*	0.200
BDI total	7.5±.4.4	9.2±6.3	5.4±4.9	8.119	2	0.0004*	0.0287*	0.0001*	0.141
BDI somatic	3.4±2.3	3.8±2.7	2.2±1.9	8.677	2	0.0003*	0.0031*	0.0003*	0.532
BDI psychic	4.1±2.9	5.4±4.1	3.2±3.6	5.418	2	0.0053*	0.2014	0.0012*	0.0847
ARS	7±5	7.8±6.3	5.02±5.6	3.883	2	0.0225*	0.0647	0.0109*	0.535

SD=standard deviation; df=degrees of freedom; MMSE=Mini Mental State Examination; RIR=Rey's 15-word test – Immediate Recall; RDR=Rey's 15-word test – Delayed Recall; CRO=Copy of the Rey-Osterrieth picture; DRO=Delayed Recall of the Rey-Osterrieth picture; SWCT=Stroop Word-Color Test; SVF=Semantic Verbal Fluency; PVF=Phonologic Verbal Fluency; WCST-SF=Wisconsin Card Sorting Test – short form; HARS=Hamilton Anxiety Rating Scale; HDRS=Hamilton Depression Rating; Scale; BDI= Beck Depression Inventory; ARS=Apathy rating scale.

Table 4.2b: Neuropsychological and Neuropsychiatric Score

	RPD (n=42) Mean±SD	LPD (n=42) Mean±SD	HC (n=84) Mean±SD	χ2	df	P
RIR (%)[a]	12 (28.6%)	13 (30.9%)	/	0.057	1	0.811
RDR (%)[a]	14 (33.3%)	11 (26.2%)	/	0.513	1	0.474
CRO (%)[a]	9 (21.4%)	10 (23.8%)	/	0.068	1	0.794
DRO (%)[a]	4 (9.5%)	5 (11.9%)	/	0.124	1	0.724
SWCT interference (%)[b]	9 (21.4%)	7 (16.7%)	/	0.309	1	0.578
SWCT word (%)[b]	9 (21.4%)	7 (16.7%)	/	0.309	1	0.578
SWCT color (%)[b]	17 (40.5%)	13 (31%)	/	0.83	1	0.362
SVF (%)[a]	8 (19.1%)	7 (16.7%)	/	0.081	1	0.776
PVF (%)[a]	11 (26.2%)	9 (21.4%)	/	0.263	1	0.608
WCST-SF categories (%)[a]	7 (16.7%)	5 (11.9%)	/	0.389	1	0.533
WCST-SF perseverative errors (%)[b]	10 (23.8%)	9 (21.4%)	/	0.068	1	0.794
WCST-SF non-perseverative errors (%)[b]	9 (21.4%)	11 (26.2%)	/	0.263	1	0.608
HDRS (%)[b]	7 (16.7%)	16 (38%)	/	4.850	1	0.0277*
HARS (%)[b]	9 (30.9%)	13 (21.4%)	/	0.985	1	0.321
BDI total (%)[b]	4 (9.5%)	13 (31%)	/	5.974	1	0.0145*
BDI somatic (%)[b]	6 (14.3%)	11 (26.2%)	/	1.844	1	0.174
BDI psychic (%)[b]	4 (9.5%)	11 (26.2%)	/	3.977	1	0.0461*
ARS (%)[b]	5 (11.7%)	7 (16.7%)	/	0.389	1	0.533

a % of patients with score ≤ 1.5 SD than HC group; b % of patients with score ≥ 1.5 SD than HC group; *Statistically significant differences.

4.1.4 Discussion

Neuropathologic [6], neuroimaging [7] and clinico-pharmacologic [8] data suggest that dopamine depletion may influence neuropsychiatric and cognitive symptoms in the early

stages of PD. The present results demonstrate, however, that body side of onset of motor symptoms does not significantly affect the pattern and severity of neuropsychiatric and neuropsychological alterations in early, unmedicated, PD patients. To our knowledge, this is the first study investigating systematically similarities and differences of both neuropsychiatric and cognitive features in unmedicated LPD vs. RPD patients by the use of rigorous psychiatric diagnostic criteria associated with specific psychopathologic and neuropsychological scales. Our results, therefore, strongly support the uncoupling between motor and non-motor (neuropsychiatric/cognitive) consequences of damage of dopaminergic nigrostriatal neurons in the early stages of PD. A trend was observed at the BDI psychic, LPD patients showing higher scores than RPD. Moreover, higher number of LPD patients as compared to RPD ones deviated from HC at depression scales. This suggests that LPD patients may suffer from slightly stronger severity of depressive symptoms unrelated to the degree of motor impairment. This slight difference between LPD and RPD patients is in line with the role of the right hemisphere in processing negative emotions, pessimistic thoughts and unconstructive thinking styles.

Our findings showing the significant impairment of several cognitive domains (verbal memory, language, complex constructional praxis, attention and executive functions) in drug naïve PD patients further confirm the presence of slight, although significant, cognitive symptoms in newly diagnosed, drug-naïve PD patients.

The lack of difference in cognitive performances between LPD and RPD patients reported

here is in contrast with previous reports showing the preferential impairment of linguistic and verbal memory functions in RPD and visual-spatial functions in LPD [review in 2]. In this respect, it is noteworthy that the majority of studies reviewed previously [2] were carried out on medicated PD patients, and in several instances, subjects in more advanced disease stage were also included. Indeed, one cannot exclude that cognitive differences between LPD or RPD patients may emerge in more advanced disease stages, particularly after development of axial motor symptoms.

In conclusion, the results of this study clearly show that body side of onset of motor symptoms does not influence the pattern or severity of neuropsychiatric and cognitive abnormalities in unmedicated PD patients. These findings support the hypothesis of uncoupling between motor and non-motor consequences of dopamine depletion in early, unmedicated, PD, and suggest that differences reported in previous reports may be secondary to interactions between disease progression and therapeutic management.

4.2 Cognitive and neuropsychiatric profile of tremor dominant and akinetic-rigid motor subtypes of newly diagnosed drug naïve Parkinson's disease patients

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4.2.1 Background

PD is a heterogeneous neurodegenerative disorder characterized by motor and non-motor symptoms. In consideration of the predominant motor features, it is possible to distinguish two main different clinical subtypes: tremor dominant (TD) and akinetic-rigid (ART). Moreover, a mixed phenotype (MIX), not presenting one prevailing motor feature could be identified [9, 10].

It has been suggested that the two motor presentations of PD, ART and TD, are characterized by a different risk and severity of specific non-motor symptoms along the disease course such as depression, apathy and cognitive problems [11,12]. In particular, ART subjects show a more rapid clinical progression and have an increased risk to develop disability and dementia [11]. On the other hand, it has been showed that the TD variant has a slower disease progression, less cognitive decline, and lower incidence of neuropsychiatric complications such as visual hallucinations and depression [13], when compared to the ART group [14-17]. These different features of the two PD motor patterns are supported by pathophysiological investigations, showing a more widespread reduction of pallidal and striatal dopamine levels in ART patients, when compared to TD ones [13].

According to our knowledge, studies conducted on newly diagnosed drug naïve PD patients, with the aim of investigating cognitive and behavioral differences between ART and TD motor subtypes in the early stage of the disease are rare and need to be explored further. In particular, it has been demonstrated that de novo drug naive patients with

postural instability/gait difficulty (PIGD) PD motor type showed significantly higher alexithymic features compared to patients of other motor types (TD and MIX) [18] and that PIGD PD presented a higher frequency of MCI respect to TD patients. However, the comparison between cognitive performances of TD and PIGD patients showed that the former outperformed the latter only in the Boston Naming Test Short Form, a test to assess language ability [19]. In line with this, Domellof and colleagues did not find significant differences in the neuropsychological variables between the PIGD and the TD phenotype patients [20].

Investigating PD motor subtypes in the early stage of the disease may provide more insight into the progression of non-motor symptoms, in particular on cognitive and psychological symptoms evolution, in order to stratify the individual prognostic risk and offer a more precise disease evolution tailored on patient subgroup.

Thus, we sought to explore in detail neuropsychological and neuropsychiatric characteristics in the very early stage of the three motor subtypes of PD (akinetic-rigid, tremor-dominant and mixed). We studied newly diagnosed drug naïve patients in order to avoid the possibility that confounding factors, such as disease duration or drug treatment, might variably affect the cognitive, psychopathological and motor results.

4.2.2 Methods

Participants

The study was carried out on 68 consecutive newly diagnosed drug naïve PD patients

diagnosed according to international guidelines (Hughes, Daniel et al. 1992). Clinical diagnoses of PD were confirmed on 12 and 24 months follow-up evaluations from symptom onset. All patients were recruited at outpatient services for movement disorders of four institutions (I.R.C.C.S. Santa Lucia Foundation, Neurological Unit of "San Giovanni Addolorata" Hospital, NESMOS Department of "Sapienza" University, Movement Disorder Unit of "Sant'Andrea" Hospital, and Department of Medicine of Systems of University "Tor Vergata", Rome, Italy). Based on different motor presentations of PD, patients were divided in three subgroups according to Kang et al. guidelines [1]: ART (n=39), TD (n=22) and MIX (n=7). Subtypes were defined according to the ratio of patient's UPDRS III tremor score (obtained as sum of Items 20 and 21 divided by 4) to her/his mean UPDRS akinetic/rigid score (sum of items 22–27 and 31 divided by 15) such that (1) a ratio = 1.0 equals tremor-dominant, (2) a ratio = 0.80 equals akinetic–rigid, and (3) a ratio between 0.80 and 1.0 equals mixed [1].

Age at symptom onset was defined as the first appearance of motor symptoms according to the patient. Duration of the disease was defined as the time between symptom onset and time of diagnosis.

Inclusion criteria were the following:

1) patients at the first diagnosis of PD, not yet undergoing antiparkinsonian therapy;

2) vision and hearing sufficient for compliance with testing procedures;

3) MMSE score ≥ 26;

4) no dementia according to the Movement Disorder Society (MDS) clinical diagnostic

criteria [5].

Exclusion criteria were:

1) presence of major non stabilized medical illnesses (i.e. diabetes, obstructive pulmonary disease or asthma, hematologic/oncologic disorders, vitamin B12 or folate deficiency, pernicious anemia, clinically significant and unstable active gastrointestinal, renal, hepatic, endocrine or cardiovascular disorders);

2) known or suspected history of alcoholism, drug dependence and abuse, head trauma and mental disorders (apart from mood or anxiety disorders) according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [21];

3) presence of vascular brain lesions, brain tumor and/or marked cortical and subcortical atrophy on CT and/or MRI scan.

The study was approved by the Ethical Committee of I.R.C.C.S. Santa Lucia Foundation and, in accordance with the Helsinki Declaration, each subject signed an informed consent form prior to enrolment.

Neurological and Psychiatric Examinations

Sociodemographic data were collected by neurologists during the clinical examination. Clinical characteristics, such as age at onset of first motor symptoms and duration of illness were also recorded. The evaluation of motor symptoms was made using the UPDRS-III [22] and disease stage was measured by the modified H&Y scale [23].

All patients underwent a Structured Clinical Interview for DSM-5 Disorders- Clinician

Version (SCID-5-CV) [24] for the identification of psychiatric disorders according to the DSM-V criteria (American Psychiatric Association [21].

Psychiatric diagnoses were made by a senior psychiatrist.

The day after completion of the baseline evaluation, all patients started antiparkinsonian treatment according to the guidelines of European Federation of Neurological Societies and MDS-European Section [25].

Neuropsychiatric and Neuropsychological assessment

All participants underwent the following neuropsychiatric scales: HDRS, HRS, TAS-20, SHAPS and ARS. Anhedonia diagnosis was based on a SHAPS cut-off score of > 2, and apathy diagnosis on Starkstein [26] criteria adapted from Marin [27].

All patients were submitted to a detailed neuropsychological evaluation including: MMSE, RIR, RDR, PVF, SVF, CRO, DRO, WCST-SF and SWCT.

All testing and clinical evaluations were carried out from trained specialists who were blind to the aims of the study. Acceptable inter-rater reliability was defined as $k>0.80$.

Statistical analysis

The distribution of the analysed factors was verified by using the Shapiro-Wilk test. Between group comparisons for sociodemographic, neurological, neuropsychiatric and neuropsychological variables were performed using ANOVA as well as, in the case of distribution that was different than normal, using Kruskal-Wallis ANOVA for continuous variables and $\chi 2$ tests for categorical variables, followed by Fisher's Protected Least

Significant Difference (PLSD) test post-hoc comparisons when appropriate.

The level of statistical significance was defined as p level less than 0.05.

4.2.3 Results

Table 4.2.1 shows the sociodemographic and clinical characteristics of the study populations. ART, TD and MIX PD subgroups did not differ significantly in any of these variables.

There were no significant differences in neuropsychiatric scores (Table 4.2.2) among ART, TD and MIX PD patients.

Table 4.2.1. Sociodemographic and neurological characteristics of ART, TR and MIX PD patients.

Characteristics	ART (n=39) Mean (SD)	TD (n=22) Mean (SD)	MIX (n=7) Mean (SD)	F	df	p
Age (years)	63.7 (9.8)	63.4 (9.8)	64.7 (12.5)	0.045	2	0.956
Age at symptom onset (years)	63.0 (9.8)	62.8 (9.7)	64.0 (12.5)	0.040	2	0.961
Duration of illness (years)	0.7 (0.5)	0.6 (0.6)	0.7 (0.5)	0.058	2	0.943
Education (years)	11.4 (4.8)	12.1 (3.7)	15.0 (2.2)	2.119	2	0.128
UPDRS-III	13.3 (8.0)	12.9 (8.1)	18.3 (10.2)	1.246	2	0.294
H&Y	1.5 (0.5)	1.4 (0.5)	1.8 (0.6)	1.852	2	0.232
	n (%)	**n (%)**	**n (%)**	**χ^2**		**p**
Gender (male)	29 (74.4)	12 (54.5)	3 (42.9)	4.049	2	0.132

PD=Parkinson's disease; ART=akinetic-rigid PD subtype; TD=tremor-dominant PD subtype; MIX=mixed PD subtype; SD=standard deviation; df=degrees of freedom; UPDRS-III=Unified Parkinson's Disease Rating Scale–Part III; H&Y=Hoehn and Yahr scale.

Table 4.2.2. Neuropsychiatric scores of ART, TR and MIX PD patients.

Variables	ART (n=39) Mean (SD)	TD (n=22) Mean (SD)	**MIX (n=7) Mean (SD)**	**F**	**df**	**p**
HDRS	7.2 (3.8)	7.2 (3.7)	9 (3.3)	0.823	2	0.444
HARS	6.8 (3.3)	7.4 (4.8)	10.0 (5.1)	1.919	2	0.155
SHAPS	0.2 (0.5)	0.2 (0.4)	0.0 (0.0)	0.850	2	0.432
ARS	6.7 (5.0)	6.7 (4.2)	10.3 (2.6)	3.971	2	0.165
TAS-20 total	44.7 (12.5)	43.9 (9.5)	46.3 (12.8)	0.108	2	0.897
TAS-20 F1	11.5 (5.6)	12.2 (5.8)	13.6 (6.1)	0.412	2	0.664
TAS-20 F2	13.0 (6.2)	12.9 (5.1)	12.1 (4.2)	0.065	2	0.937
TAS-20 F3	20.2 (5.6)	18.8 (5.6)	20.6 (4.9)	0.525	2	0.594

PD=Parkinson's disease; ART=akinetic-rigid PD subtype; TD=tremor-dominant PD subtype; MIX=mixed PD subtype; SD=standard deviation; df=degrees of freedom; HDRS=Hamilton Depression Rating Scale; HARS=Hamilton Anxiety Rating Scale; SHAPS=Snaith-Hamilton Rating Scale; ARS=Apathy Rating Scale; TAS-20=Toronto Alexithymia Scale-20 item; TAS-20 F1=TAS-20 difficulty identifying feelings; TAS-20 F2=TAS-20 difficulty describing feelings; TAS-20 F3=TAS-20 externally oriented thinking.

The three groups of PD patients did not significantly differ in neuropsychological scores (Table 4.2.3).

Table 4.2.3. Neuropsychological scores of ART, TR and MIX PD patients.

Variables	ART (n=39) Mean (SD)	TD (n=22) Mean (SD)	MIX (n=7) Mean (SD)	F	df	p
MMSE	28.5 (2.0)	28.9 (1.4)	29.4(1.1)	0.986	2	0.379
RIR	38.3 (11.1)	40.9 (12.4)	37.6 (8.3)	0.420	2	0.658
RDR	7.9 (3.7)	8.8 (4.0)	7.4 (2.7)	0.599	2	0.552
CRO	29.1 (6.1)	30.0 (5.4)	31.4 (3.6)	0.578	2	0.564
DRO	16.2 (6.5)	17.1 (7.1)	13.1(6.6)	0.978	2	0.382
SWCT-word reading (sec)	15.8 (5.4)	14.4 (2.8)	14.7 (2.9)	0.705	2	0.498
SWCT-color naming (sec)	21.4 (8.1)	19.6 (4.4)	20.7 (4.0)	0.491	2	0.614
SWCT-interference time (sec)	42.0 (13.0)	38.5 (11.8)	38.6 (14.2)	0.620	2	0.541
WCST-SF categories	5.4 (1.3)	5.5 (1.1)	6.0 (0.0)	0.717	2	0.492
WCST-SF Perseverative errors	2.7 (3.7)	2.5 (4.4)	1.4 (0.8)	0.347	2	0.708
WCST-SF Non perseverative errors	3.0 (2.9)	2.0 (2.8)	1.6 (1.1)	1.245	2	0.295
PVF	30.7 (11.7)	36.3 (10.8)	34.6 (11.1)	1.780	2	0.177
SVF	20.1 (5.1)	21.5 (5.1)	21.1 (4.8)	0.546	2	0.582

PD=Parkinson's disease; ART=akinetic-rigid PD subtype; TD=tremor-dominant PD subtype; MIX=mixed PD subtype; SD=standard deviation; df=degrees of freedom; RIR=Rey's 15-word test - Immediate Recall; RDR=Rey's 15-word test - Delayed Recall; CRO=Copy of the Rey-Osterrieth picture; DRO=Delayed Recall of the Rey-Osterrieth picture; SWCT=Stroop Word-Color Test; WCST-SF=Wisconsin Card Sorting Test – short form; PVF=Phonologic Verbal Fluency; SVF=Semantic Verbal Fluency. *Statistically significant difference

4.2.4 Discussion

We investigated the complete neuropsychiatric and neuropsychological profile associated with motor subtypes of PD in newly diagnosed drug naïve PD patients. Analysing this

population, we had the opportunity to investigate the cognitive and psychopathological aspects without confounding factors, such as disease duration or drug treatment, that might affect results. Although previous studies have shown a worse cognitive and psychopathological profile of ART than TD patients [14, 16, 18, 28, 29], the main finding of our study demonstrates the absence of any cognitive-affective dissimilarities in PD motor subtypes groups at the time of the clinical motor onset.

Most likely, in the early stage of illness cognitive and neuropsychiatric differences from ART PD patients are subthreshold, suggesting that such a non-motor symptoms profile becomes clinically evident with the progression of PD. This idea is supported, at least to the cognitive aspect, by two studies conducted on de novo drug naïve PD patients that did not find differences in cognitive profile between PIGD PD motor subtype and TD subtype. However, one study found that PIGD patients were more alexithymic than TD ones. This discrepancy is probably due to the fact that in our study PD patients have a really short duration of illness (less than 1 year) and to the different method to classify motor subtypes that has been used.

The major strength of the present study is the nature of the population investigated (i.e. newly diagnosed drug naïve ART PD and TD PD patients). In fact, since dopamine replacement therapy may influence or mask neuropsychiatric and cognitive symptoms, studying a group of PD patients transiently drug free allows a more naturalistic picture. Additional strength is the classification of Kang et al. that we utilized in order to identify motor subtypes of PD. Indeed, this methods seems to be the most adequate in the early phase of PD, whereas other

classifications [19] consider other hallmarks, such as falls and postural instability, that are more frequent in moderate and advanced stages of PD. Finally, the comprehensive neuropsychiatric and neuropsychological battery that we used represents a further innovative approach.

We also acknowledge some limitations of our study. First, the diagnosis of our patients has not been confirmed by pathological evidence, but it was given only by positive response to dopaminergic therapy. However, the diagnosis is likely to be correct, since all patients were diagnosed by two independent movement disorders specialists, both at baseline and at follow-up visits performed after 12 and 24 months, when the effect of dopaminergic treatment can be evaluated. Second, as far the assessment of motor symptoms it was based on the clinical judgment of investigators. More objective motor measures may give a better description of patients' disabilities.

In conclusion, we showed that in the early stage of PD, motor subtypes are not associated with a specific cognitive or neuropsychiatric profile, suggesting that a possible cognitive-affective differentiation emerges only with the progression of the disease and potentially with its interaction with DRT. Therefore, neuropsychological and behavioral evolutions are not predictable based on early motor presentation and regular follow-ups are needed to investigate their different possible progression. Further studies investigating at which point of the disease course the motor subtypes start to diverge are needed.

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5. Early PD patients

5.1 Neuropsychiatric and Cognitive profile of early Richardson's syndrome, Progressive Supranuclear Palsy-parkinsonism and Parkinson's disease

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5.1.1 Background

Progressive Supranuclear Palsy (PSP) is the second most common degenerative parkinsonism after idiopathic PD (PD) [1]. Despite of profound neuropathologic differences, PSP and PD share similar features, including bradykinesia, loss of dexterity and gait disturbances that may complicate differential diagnosis particularly early along disease course. Further increasing the diagnostic challenge, recent clinic pathological data distinguished several clinical phenotypes of PSP including the PSP-parkinsonism (PSP-P), characterized by asymmetric onset of symptoms, tremor, early bradykinesia, non-axial dystonia and a response to levodopa, that more closely overlaps with PD than the classic description of 'Richardson's syndrome' (PSP-RS) [2].

PSP patients in the advanced stages consistently suffer from more severe affective and cognitive symptoms, including apathy, depression, executive and visual-spatial deficits, than patients with PD [3,4]. The question arises as to whether differences of the pattern and severity of neuropsychiatric and neuropsychological symptoms among PD, PSP-P and PSP-RS are precociously detectable, along the time span of potential motor symptom overlap.

The results of previous studies are rather contradictory [5-7]. Aarsland et al. described increased apathy and disinhibition in PSP patients in comparison with PD patients [5]. Lee et al. [6] reported more robust impairment of verbal memory and processing, planning and set-shifting in a small cohort of PSP with respect to PD patients, all recruited within

the first five years of the illness. Conversely, Borroni et al. [7] found similar neuropsychiatric and neuropsychological features in patients suffering from several degenerative parkinsonisms (PD, PSP, corticobasal degeneration, dementia with Lewy bodies). Data concerning a shorter frame time after onset of motor symptoms are, however, missing. Further, a detailed investigation using a complete neuropsychiatric and cognitive battery in early PSP-P and PSP-RS patients is still lacking.

The aim of this study was to investigate comprehensive neuropsychiatric and cognitive profile in PSP-P and PSP-RS patients examined within 24 months from motor symptom onset, and to compare possible dysfunctions with those found in PD. We hypothesized that discrete neuropsychiatric and neuropsychological profiles may be identified in early phases of PSP-RS, PSP-P and PD.

5.1.2 Methods

Participants

The study was carried out on 180 consecutive patients. Inclusion criteria were:

a) age between 40-80 years;

b) diagnosis of degenerative parkinsonism (i.e., PD, PSP-RS and PSP-P), with onset of symptoms dating less than 24 months at enrollment.

Patients were recruited during scheduled visits at the Outpatient Services for Movement Disorders of our Institutions in the period between May 2006 and January 2014.

Exclusion criteria were:

a) co-morbidity with major, not stabilized, medical illnesses;

b) known or suspected history of alcoholism, drug dependence or abuse, other neurological disorders, head trauma and mental disorders (apart from mood and anxiety disorders) according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition - Text Revision (DSM-IV-TR) [8];

c) presence of vascular brain lesion or neoplasm at CT or MRI brain scan;

d) noncompliance with testing procedure.

All patients were regularly followed-up in our outpatient clinics. Clinical diagnosis of either PD (n=155) or PSP (n=25) were confirmed over a minimum of three years follow-up from symptom onset, according to the criteria by Gelb et al. [9] and Litvan et al. [1]. Specifically, according to diagnostic proposal of PSP phenotypes by Williams et al. [2,10], that is currently the reference classification to distinguish between PSP-P and PSP-RS, 14 patients were classified as PSP-RS since falls, supranuclear gaze palsy, postural instability and levodopa resistance were the predominant clinical features within the first 24 months from symptoms onset; eleven patients were classified as PSP-P as they showed in the first 24 months of the disease abnormality of saccadic eye movements, positive response to levodopa, asymmetric onset and postural instability. After a minimum of three years follow-up, phenotype of PSP-P patients more closely overlapped the PSP-RS patients with severe postural instability (11/11), falls (7/11), supranuclear gaze palsy (11/11) and

abnormal saccades (11/11) (Table 5.1.1b).

Dopamine replacement therapy dosages were calculated as daily levodopa equivalents. The following conversion table was applied: 100 mg levodopa = 1 mg pramipexole = 5 mg ropinirole = 5 mg rotigotine. Within each group, the number (and %) of subjects receiving antidepressant, benzodiazepines and/or antipsychotic therapy was calculated.

The protocol was approved by the Ethical Committee of the Santa Lucia Foundation IRCCS, and each subject signed the informed consent before enrollment.

Sociodemografic and clinical assessment.

The demographic and neurological features of patients were collected at enrollment by neurologists with expertise on parkinsonisms. The severity of motor symptoms was measured by UPDRS-III.

Within 2 weeks from enrollment, all subjects underwent a SCID-P. Apathy was diagnosed according to the adaptation by Starkstein [12] of the Marin criteria [13]. All psychiatric diagnoses were made by a senior psychiatrist.

All participants underwent the following neuropsychiatric scales: HARS, BDI (total score; psychic and somatic sub-scores), ARS, PPRS.

All patients were submitted to a detailed neuropsychological evaluation including: MMSE, RIR, RDR, PVF, SVF, CRO, DRO, SWCT,

All tests have been described in details elsewhere [11].

Neuropsychiatric symptom severity and neuropsychological performances were assessed by 3 trained neuropsychologists. Acceptable inter-rater reliability was defined as k>0.80.

Ancillary assessment of emotion recognition and executive functions

We also assessed the recognition of facial emotion expressions and executive functions to investigate some cognitive and behavioral features possibly linked to apathy. The Penn Emotion Recognition Test (PERT) was used to assess facial emotion recognition ability. This is a standardized and validated test [14] of 96 color photographs of facial expressions of five emotions (happiness, sadness, anger, fear, disgust) and neutral faces. The participants viewed the pictures of the facial expressions on the computer screen. Then, they had to label the basic emotions by choosing one out of the six possibilities (i.e., anger, sadness, disgust, fear, happiness, neutral).

WCST-SF was used to explore executive function. Data on PERT and WCST-SF were available only for a subset of the study sample. In particular, 138 PD, 9 PSP-P and 9 PSP-RS patients underwent the PERT examination and 154 PD, 11 PSP-P and 11 PSP-RS patients the WCST-SF. These data were analyzed only in relationship with apathy.

Statistical analysis

Differences in demographic, clinical, neuropsychiatric and neuropsychological features among groups were assessed by the chi-squared test for categorical variables and by a series of Kruskal-Wallis H tests for continuous variables followed by Mann-Whitney U test post-hoc comparisons when appropriate. The neuropsychiatric and neuropsychological

independent variables that differed significantly after Bonferroni's correction for multiple comparisons (n=13; i.e., BDI psychic, BDI somatic, HARS, ARS, RIR, RDR, CRO, DRO, PVF, SVF, SWCT word reading, SWCT color naming, SWCT interference time; $p<0.05/13= p<0.0038$) among groups were then included in a multivariate logistic regression analysis to identify predictors of PSP subtype diagnosis (considered as dependent variable). The reference category was diagnosis of PD.

Further, as an ancillary analysis, we ran a multivariate logistic regression analysis, considering PSP-P, PSP-RS and PD diagnosis as dependent variables and including as independent variables both neuropsychiatric categorical variables (i.e., diagnosis of depression and/or apathy) that were significantly different among groups and the predictor(s) selected by the former regression model. Again the reference category was diagnosis of PD.

Finally, in an explorative analysis, differences among groups in scores of PERT and WCST-SF were assessed by a series of Kruskal-Wallis H tests followed by Mann-Whitney U test post-hoc comparisons when appropriate. The Spearman's rank-order correlation coefficient was computed in each group (i.e., PD, PSP-P, PSP-RS) to assess the relationship between ARS score and WCST-SF scores. Given the exploratory nature of these last analyses, correction for multiple comparisons was not applied and the level of statistical significance was accepted as p less than 0.05.

5.1.3 Results

Demographic and clinical features of the study cohort

The three groups did not differ significantly in any demographic and clinical features (Table 5.1.1a), apart from UPDRS-III score that was higher in PSP-RS patients in comparison with PD patients (Table 5.1.1a).

Table 5.1.1a: Demographic and clinical features of patients with PD, PSP-P and PSP-RS.

	PD (n=155)	PSP-P (n=11)	PSP-RS (n=14)	H	df	Kruskal-Wallis P	Post Hoc analysis (Mann-Whitney)		
							P PD vs. PSP-P	P PD vs. PSP-RS	P PSP-P vs. PSP-RS
Age (years)	67.2±7.47 (91.197)	65.4±6.6 (69.273)	68.9±7.5 (99.464)	2.268	2	0.322	na	na	na
Disease duration (months)	15.3±8.4 (88.971)	15.3±9.4 (89.682)	18.75±5.2 (108.07)	1.728	2	0.421	na	na	na
Education (years)	10.5±4.5 (90.926)	11.9±5.2 (107.136)	8.8±3.9 (72.714)	2.763	2	0.251	na	na	na
UPDRS-III score	15.9±9.3 (82.224)	21.2±11.3 (107.944)	25.0±6.5 (134.000)	10.184	2	0.006	0.127	0.004	0.229
Levodopa (mg/day)	95.2±148.1 (90.045)	172.7±214.9 (106.136)	62.5±122.8 (83.250)	1.273	2	0.529	na	na	na
Dopamine Agonist Equivalents (mg/day)	85.1±130 (92.803)	140.9±253.8 (94.227)	7.1±26.7 (62.071)	4.527	2	0.104	na	na	na
Levodopa Equivalents (mg/day)	180.3±188.5 (92.010)	313.6±406.3 (106.136)	69.6±143.5 (61.500)	5.457	2	0.065	na	na	na
	PD	PSP-P	PSP-RS	χ2	df	P			
Sex (male, %)	84 (54,2%)	7 (63%)	6 (42,8%)	1.117	2	0.573	na	na	na
Under Antidepressant drugs n (%)	15 (9.7%)	2 (18.2%)	4 (28.6%)	4.930	2	0.085	na	na	na
Under Benzodiazepine n (%)	21 (13.5%)	1 (9.1%)	1 (7.1%)	0.616	2	0.735	na	na	na
Under Antipsychotic drugs n (%)	2 (1.3%)	0 (0%)	1 (7.1%)	2.882	2	0.237	na	na	na

Table 5.1.1b: Demographic and clinical features of patients with PD, PSP-P and PSP-RS.

Clinical features of PSP patients				
	PSP-RS T0 (n = 14)	PSP-RS T1 (n = 14)	PSP-P T0 (n = 11)	PSP-P T1 (n = 11)
Falls	12 (85.7%)	14 (100%)	0 (0%)	7 (63%)
Postural Instability	14 (100%)	14 (100%)	3 (30%)	11 (100%)
Supranuclear gaze palsy	14 (100%)	14 (100%)	2 (18%)	11 (100%)
Abnormal saccades	14 (100%)	14 (100%)	7 (63%)	11 (100%)
Asymmetric symptoms	2 (14%)	1 (7%)	9 (85%)	6 (54%)
Response to Levodopa	2 (14%)	0 (0%)	6 (54%)	2 (18%)
Speech disturbance	8 (57%)	11 (78%)	3 (30%)	6 (54%)

Data represent mean±SD (Mean Rank); na= not applicable.

T0=within 24 months from motor symptoms onset; T1= ≥ three years follow-up from symptom onset.

Neuropsychiatric rating scales

Table 5.1.2 shows the results of neuropsychiatric rating scales represented by continuous values. The three groups differed significantly only in the ARS score. PD patients scored better than other two groups. Differences among groups at BDI scores did not survive after corrections for multiple comparisons.

Table 5.1.2: Neuropsychiatric evaluation and frequency of neuropsychiatric diagnoses of patients with PD, PSP-P and PSP-RS.

	PD (n=155)	PSP-P (n=11)	PSP-RS (n=14)	H	df	Kruskal-Wallis P	Post Hoc analysis (Mann-Whitney)		
							P PD vs. PSP-P	P PD vs. PSP-RS	P PSP-P vs. PSP-RS
BDI total	8.4±6.4 (86.210)	10.5±5.2 (114.045)	13.6±9 (119.500)	7.634	2	0.022	0.08	0.02	0.584
BDI psychic	4.9±4.5 (85.723)	6.7±3.6 (116.409)	8.4±5.7(123.036)	9.481	2	0.009	0.054	0.011	0.529
BDI somatic	3.4±2.6 (88.010)	3.8±2.1 (100.182)	5.1±4 (110.464)	2.789	2	0.248	na	na	na
HARS	8.4±4.9 (89.516)	8.4±2.9 (96.682)	9.0±5 (96.536)	0.398	2	0.820	na	na	na
ARS	8.04±6.3 (83.606)	14±9.5 (118.500)	19.4±9.6 (144.821)	21.105	2	<0.0001*	0.032	<0.0001	0.218
PPRS	6.819±1.187 (87.577)	7±0.894 (105.227)	7.385±1.446 (106.000)	2.528	2	0.282	na	na	na
	PD	PSP-P	PSP-RS	$\chi 2$	df	P			
Depression (Y) (% Y)	51 (32.9%)	7 (63.6%)	9 (64.3%)	8.91	2	0.012	na	na	na
Anxiety (Y) (% Y)	16 (10.3%)	0 (0%)	1 (7.1%)	1.374	2	0.503	na	na	na
Apathy (Y) (% Y)	4 (2.6%)	3 (27.3%)	3 (21.4%)	19.225	2	<0.0001	na	na	na

Data represent mean±SD (Mean Rank). BDI = Beck Depression Inventory; HARS = Hamilton Anxiety Rating Scale; ARS = Apathy Rating Scale; PPRS = Parkinson's Psychosis Rating Scale. * Significant after Bonferroni's correction for multiple comparisons (n=13); p<0.05/13= p<0.0038; na= not applicable.

Predictors of PSP diagnosis

Based on the results of Kruskal-Wallis H tests, we included in the logistic regression analysis as potential predictors of PSP subtypes the ARS, RIR, CRO, PVF, SVF and SWCT scores. MMSE score was not included, being an index of global cognitive functioning. In this logistic regression model, PVF score (OR=0.844, 95%CI=0.742–0.960; p=0.0096) significantly predicted PSP-RS diagnosis. ARS score only approached significance in predicting PSP-P diagnosis (OR=1.09, 95%CI=0.995–1.21; p=0.06). In a second multivariate logistic regression model, we included as independent predictors of PSP subtypes the neuropsychiatric diagnoses of apathy and depression and PVF score, being the only cognitive predictor identified by the first logistic regression model. In accordance with the results of the previous multivariate logistic regression model, PVF score (OR=0.769, 95%CI=0.680–0.870; p<0.0001) significantly predicted PSP-RS diagnosis. The diagnosis of apathy (OR=9.360, 95%CI=1.654–52.956; p=0.0114) significantly predicted the PSP-P diagnosis.

Ancillary analysis: emotion recognition and executive functions

PSP-RS patients scored worse than PD at all WCST-SF sub-scores. Further, PSP-RS displayed worse score than PSP-P at WCST-SF non-perseverative errors and achieved categories. No differences emerged between PD and PSP-P patients (Table 5.1.4).

Table 5.1.4 shows results of facial emotion recognition of PD, PSP-P and PSP-RS. The three diagnostic groups differed significantly in the recognition of facial emotions

expressing sadness and in the recognition of neutral faces. PSP-RS patients failed in recognizing sadness compared to both PD and PSP-P patients. PD patients recognized better than PSP-P neutral faces.

Additionally, we performed a Spearman's rank-order correlation splitted by group (i.e., PD, PSP-P, PSP-RS patients) to assess the relationship between ARS score and WCST-SF sub-scores. In PSP-RS group, we found significant correlations between ARS score and WCST-SF non-perseverative errors (Rho=0.775, p=0.014), between ARS score and WCST-SF perseverative errors (Rho=0.791, p=0.12) and between ARS score and WCST-SF achieved categories (Rho=-0.773, p=0.014). No significant correlations were found in PSP-P group. In PD group, the only significant correlation observed was between ARS score and WCST-SF non-perseverative errors (Rho=0.165, p=0.04).

Table 5.1.4: Ancillary data on executive functions and facial emotion recognition of patients with PD, PSP-P and PSP-RS.

	PD (n=154)	PSP-P (n=11)	PSP-RS (n=11)	H	df	Kruskal-Wallis P	Post Hoc analysis (Mann-Whitney)		
							P PD vs. PSP-P	P PD vs. PSP-RS	P PSP-P vs. PSP-RS
WCST-SF perseverative errors	3.19±4.27 (85.851)	3.64±5.22 (86.545)	7.46±7.26 (127.545)	6.893	2	0.032	0.966	0.009	0.07
WCST-SF non-perseverative errors	3.14±2.77 (86.146)	2.72±2.24 (81.409)	6.55±4.85 (128.545)	7.337	2	0.025	0.781	0.008	0.020
WCST-SF categories	5.36±1.21 (90.692)	5.55±1.04 (99.045)	3.64± 2.34 (47.273)	7.958	2	0.019	0.594	0.006	0.024
	PD (n=138)	PSP-P (n=9)	PSP-RS (n=9)	H	df	Kruskal-Wallis P	Post Hoc analysis (Mann-Whitney)		
							P PD vs. PSP-P	P PD vs. PSP-RS	P PSP-P vs. PSP-RS
Anger	8.09±2.33 (79.054)	7.89±1.69 (74.611)	8.0±2.35 (73.889)	0.181	2	0.913	na	na	na
Sadness	9.42±3.55 (81.529)	9.89±3.06 (84.278)	4.78± 2.39 (26.278)	12.793	2	0.002	0.878	0.0004	0.004
Disgust	6.61±2.98 (78.942)	6.22± 2.64 (75.500)	6.33± 3.28 (74.722)	0.116	2	0.944	na	na	na
Fear	8.32±3.01 (79.996)	7.89± 1.76 (71.833)	7.11± 3.10 (62.222)	1.516	2	0.469	na	na	na
Happiness	15.15±1.32 (80.725)	15.11±0.93 (72.111)	13.00±3.91 (50.778)	3.903	2	0.142	na	na	na
Neutral	10.82±3.89 (82.199)	7.78± 3.67 (47.722)	8.22± 4.02 (52.556)	8.071	2	0.018	0.027	0.06	0.791

WCST-SF = Wisconsin Card Sorting Test-short form.

5.1.4 Discussion

Our results confirm the hypothesis that PSP-P, PSP-RS and PD patients are well characterized by peculiar patterns of neuropsychiatric and cognitive symptoms detectable from the very early stages of the disease. It is of fundamental importance to highlight that the differential diagnosis among these disorders is frequently complicated at the onset by the overlap of motor symptoms of parkinsonism. Few data are available on this topic in patients with PSP-P and PSP-RS. Here, we applied to our cohort a comprehensive neuropsychological and neuropsychiatric battery and a formal psychiatric diagnosis, as opposed to previous studies [7,15,16]. In this context, our results clearly indicate that, within 24 months from onset of symptoms, there is a continuum of severity from the milder PD, throughout PSP-P, to PSP-RS. In particular, a poor performance in phonologic verbal fluency may be supportive of a diagnosis of PSP-RS, whereas the presence of apathy may predict PSP-P subtype.

Our findings enhance the previous observation by Lee et al. [6] of more robust impairment of verbal memory and processing, planning and set-shifting in PSP as compared to PD patients, by showing that significant neuropsychological differences between the two disorders may be identified already in the first 24 months after symptom's onset. Conversely, our findings appear in contrast with those by Borroni et al. [7], who reported similar patterns of neuropsychiatric and cognitive alterations among patients recruited in the early stages of different degenerative parkinsonisms

(i.e., PD, PSP, corticobasal degeneration, dementia with Lewy bodies). Several factors, including the study design, inclusion/exclusion criteria, and the methodologies applied, may contribute at justifying these discrepancies. The study by Borroni et al. [7] was designed to identify possible differential patterns of neuropsychiatric and/or cognitive symptoms in patients affected by degenerative parkinsonisms matched for global condition (MMSE score), whereas we enrolled consecutive patients to get a more naturalistic picture of the neuropsychiatric/cognitive features in PSP-RS, PSP-P and PD, with the aim of identifying quantitative and qualitative differences precociously during disease course. Depression, apathy, executive and visual-spatial impairments were, indeed, identified as core neuropsychiatric and neuropsychological features of early PSP and PD in both studies, however our investigation demonstrates the higher prevalence and severity of these symptoms in very early PSP-RS and PSP-P as compared to PD subjects.

Our data add insights into the clinical variability among patients with the two main subtypes of PSP. This is line with *post-mortem* pathological studies indicating that differences in regional burden of tau pathology account for the clinical heterogeneity observed in patients with PSP-RS and PSP-P [17,18]. Indeed, patients with PSP-P had less severe tau pathology than those with PSP-RS, milder symptomatological presentations and relatively better prognosis. Therefore, as stated by Williams and Lees [10], PSP-P and PSP-RS represent two separate points on a spectrum of clinical

features related to PSP tau pathology. We demonstrate that this assumption is reflected by neuropsychiatric and cognitive characteristics as well, PSP-P exhibiting milder clinical phenotype than PSP-RS. Following the notion that apathy represents one of the most important clinical features of patients with PSP [5], PSP-RS and PSP-P did not differ as to severity of continuous score of apathy but a higher frequency of formal apathy diagnosis was observed in PSP-P patients. Accordingly, the clinical definition of apathy conceptualized by Marin [13] and further adapted by Starkstein [12], recognizes behavioral, cognitive and emotional symptoms reflecting disruption of distinct aspects of goal directed behavior (GDB) and includes both a lack of inward emotional experience and a reduced expression of emotion. GDB impairment is sustained by the inability to flexible shifting between behaviors and to maintaining purposeful behaviors despite internal or external distractors. Consequently, since the cognitive control has been demonstrated as one substrate of apathy itself, reduced cognitive flexibility may be one contributor to higher levels of apathy [19]. Nevertheless, apathy could not been conceptualize merely as a lack of flexibility but rather as a complex process in which emotional and executive impairments contribute. Hence, our data demonstrated that PSP-RS patients are more compromised in both components. Further, our ancillary data indicated that in PSP-RS apathy is correlated whit impaired executive functions. Interestingly, PSP-RS and PSP-P patients did not show differences in WCST-SF perseverative errors, a

component that better describes the cognitive flexibility and is more closely related to the ability to respond to changing goals. The underlying mechanisms responsible for apathy may be seen as dysfunctions occurring at the level of structures sustaining elaboration, execution and control of GDB, such as prefrontal cortex (PFC) and basal ganglia [20]. Actually, neuropathological [21] and *in vivo* imaging studies [22,23] in PSP patients, assessed globally as a single disorder, demonstrated dorsal striatum, thalamus and midbrain atrophy, cortical atrophy of prefrontal areas and connectivity disruption within networks linking brainstem, basal ganglia and cortex. Based on cognitive and neuropsychiatric evaluations, our results suggest that the clinical hallmarks of such anatomical substrates may be detectable from the very early stages of the disease. However, correlation with imaging data goes beyond the purpose of our investigation.

Within this frame of a functional "prefrontal-like" syndrome, interestingly the predictor of PSP-RS diagnosis was PVF impairment, measured by a test of linguistic abilities that represents also a task of self-activation of cognitive strategies. Indeed, the dorsolateral PFC is involved in executive functions as well as in phonological processing during word generation (Brodmann Area 46) [24,25]. The correct functioning of verbal fluency is associated with activation of a diffuse cortical network [26,27]. Schofield and collaborators [27] demonstrated, by neuroimaging techniques in confirmed pathological cases of PSP, that cortical atrophy and frontal lobe tau

pathology are more severe in PSP-RS than in PSP-P patients. Rittman and colleagues recently demonstrated that verbal fluency distinguishes between PSP and PD with high sensitivity and high specificity [28]. Our results extend previous reports [28-30] showing that verbal fluency tests discriminated well between PSP-RS and PD patients already in the first 24 months of the disease.

In our cohort, PSP-RS patients displayed higher prevalence and severity (although statistically only at an uncorrected level) of depression as compared to PD cases. Nevertheless, it is of interest that neither severity of depressive symptoms nor clinical diagnoses of depression were definitive predictors of PSP-RS diagnosis. This advocates for a distinct nature of apathy and depression in PSP, rather than the former being a symptom of the latter and stresses the impairment of affective and emotional tone since the very early stages in PSP patients. Indeed, our ancillary results on emotion processing indicate that the impairment of facial emotion recognition of sadness characterizes PSP-RS patients. Nevertheless, PSP-P patients showed a worse performance of PD on the recognition of neutral faces due to the attribution of emotional saliency to unrecognized neutral expressions. These results further clarify our previous observation of compromised emotion processing in PSP and PD patients [14]. In fact, on the light of these new results, the difference in emotion recognition we have previously described between PD and PSP patients seems to be driven by PSP-RS group. In our previous study, we found that PSP patients displayed significantly

lower recognition of happy emotional faces. This result did not emerge here. Given the shorter disease duration we considered in the present study, we can speculate that the impairment in the happiness recognition emerge later in the disease course. Taken together these precocious deficits in facial emotion recognition could determinate the early difficulties on social and relational abilities.

We also acknowledge the limitations of our study. Our PSP patients were enrolled within Movement Disorders Outpatient Services, suggesting the presence of predominant "motor" phenotype of the disease, and therefore possibly underestimating the global prevalence and severity of cognitive and behavioral impairment in the early PSP population. However, this was indeed our main purpose, that is to establish if peculiar neuropsychiatric and neuropsychological profiles may precociously help in the differential diagnosis among patient with atypical parkinsonism, when very often motor profiles are overlapping. Further, here we did not administer behavioral scales to both patients and caregivers. Thus the caregiver point of view is lacking in the present study. The relative small sample size of PSP-P and PSP-RS patients advocates for further studies on larger series to confirm our findings. Finally, we do not have autoptic confirmation of our diagnosis.

In conclusion, our study demonstrates a different severity of neuropsychiatric and cognitive symptoms in PSP-P and PSP-RS with respect to PD, recruited within 24 months after onset of clinical symptoms. Specifically, we found that verbal fluency

impairment and apathy diagnosis are more supportive of diagnosis of PSP-RS and PSP-P respectively, rather than PD, within 24 months after disease onset. These findings indicate that comprehensive cognitive and psychiatric evaluations might be useful and cost-effective contributors to the diagnostic work-up of patients with progressive parkinsonism in the very early stages.

5.2. Affective impairment and emotional tone of early Richardson's syndrome and Progressive Supranuclear Palsy-parkinsonism: the role of Alexithymia and Anhedonia

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5.2.1 Background

PSP is one of the most common forms of neurodegenerative atypical parkinsonism [1, 31]. Two main clinical subtypes of PSP are described: Richardson's syndrome (PSP-RS), characterized by prominent postural instability, supranuclear vertical gaze palsy and frontal dysfunction, and PSP-parkinsonism (PSP-P) in which the prominent features are asymmetric onset, tremor and moderate initial therapeutic response to levodopa [32]. Patients with PSP display also several non-motor symptoms, such as cognitive dysfunction [33], neuropsychiatric disorders [34, 35], pain [36], gastrointestinal symptoms, fatigue [4], and sleep disorders [37, 38]. Motor and non-motor symptoms may result in significant disability and have an impact on health-related quality of life (HRQoL) of patients and their care-givers [39].

Among all non-motor symptoms that may affect PSP patients, alexithymia and anhedonia have not yet been investigated in PSP nor in the two main subtypes of PSP. Anhedonia, defined as lowered ability to experience physical or social pleasure, and alexithymia, defined as difficulty in identifying and describing feelings and distinguishing feelings from bodily sensations of emotional arousal, are two affective symptoms frequently reported in PD patients as secondary phenomenon linked to depression and apathy severity. In patients with PD these symptoms may arise as a primary characteristic [40-43] and they seem to be linked to frontal lobe dysregulation. Emotional processing and hedonic ability have a regulatory function on the

mechanisms of motivation by promoting transgenerational relationships and modulating individual behaviors aimed at increasing the individual's chances of adapting to a community. In patients with PD, these phenomena may have more than just theoretical importance and may further complicate the disease, resulting in poorer quality of life and reduced social interactions.

Frontal-subcortical dysfunction play an important role also in the PSP neuropathology [44], however no study at present investigated the frequency and severity of alexithymia and anhedonia in PSP. Consequently data comparing these symptoms between PSP and PD patients or indicating if these two emotional phenomena differentiate PSP-RS from PSP-P are lacking.

On the bases of this background, the aim of this study was to analyze the occurrence of alexithymia and anhedonia in PSP-RS and PSP-P compared to PD, early in the disease course.

5.2.2 Methods

Participants

We enrolled 155 PD, and 25 PSP aged 40-80 years, diagnosed as suffering from degenerative parkinsonism, with onset of motor symptoms dating less than 24 months at enrollment. All patients were regularly followed in our outpatient clinics. Clinical diagnosis of either PD or PSP were confirmed over a minimum of three years follow-

up from symptom onset, according to the criteria by Gelb et al. [9] and Litvan et al. [45]. Patients were classified as being affected by PSP-P (n=11) or PSP-RS (n=14) according to the criteria of Williams and colleagues [2, 10].

Patients with co-morbidity for major not stabilized medical illnesses, known or suspected history of alcoholism, drug dependence or abuse, other neurological disorders, head trauma and mental disorders (apart from mood and anxiety disorders) according to the DSM-IV-TR [46], and presence of vascular brain lesion or neoplasm at CT or MRI brain scan were excluded from the study.

Dopamine replacement therapy dosages were calculated as daily levodopa equivalents. The following conversion table was applied: 100 mg levodopa = 1 mg pramipexole = 5 mg ropinirole = 5 mg rotigotine.

The protocol was approved by the Ethical Committee of the Fondazione Santa Lucia IRCCS - Rome, and each subject signed the informed consent before enrollment.

Clinical, neuropsychiatric and neuropsychological examinations

Within 2 weeks from enrollment, all participants underwent complete clinical, neuropsychiatric and neuropsychological evaluations [see section 5.1.2].

In this study we submitted PSP and PD patients to an additional neuropsychiatric evaluation to investigate alexithymia and anhedonia. In particular, hedonic tone was evaluated using the SHAPS and alexithymia was assessed by the TAS-20.

Neuropsychiatric and neuropsychological evaluations were performed by 3 trained

neuropsychologists. Acceptable inter-rater reliability was defined as k>0.80.

Statistical analysis

Differences in sociodemographic and neuropsychiatric features among groups were assessed by the chi-squared test for categorical variables and by a series of univariate analyses of variance (ANOVAs) for continuous variables followed by Fisher's Least Significant Difference (LSD) test post-hoc comparisons when appropriate.

The level of statistical significance was defined as $p < 0.05$.

5.2.3 Results

Demographic, clinical, neuropsychiatric and cognitive features of the study cohort

The three groups did not differ significantly in any demographic feature apart from UPDRS-III that was higher in PSP-RS patients in comparison with PD patients (Table 5.2.1). As we have previously described in the same cohort in our antecedent study (for details, see 5.1.3), the three groups differed significantly in the apathethic symptoms severity and in several neuropsychological domains. PSP-RS were more depressed than two other groups and the diagnosis of apathy were more frequent in both PSP subtype diagnoses respect to PD patients.

Table 5.2.1 Demographic and clinical characteristics of patients with PD, PSP-P and PSP RS.

Characteristics	PD (n=155)	PSP-P (n=11)	PSP-RS (n=14)	F	df	ANOVA P	Post Hoc analysis (PLSD)		
							P PD vs. PSP-P	P PD vs. PSP-RS	P PSP-P vs. PSP-RS
Age (Years)	67.2±7.47	65.4±6.6	68.9±7.5	0.714	2	0.491	Na	Na	na
Disease duration (months)	15.3±8.4	15.3±9.4	18.75±5.2	1.169	2	0.313	Na	Na	na
Education (Years)	10.5±4.5	11.9±5.2	8.8±3.9	1.524	2	0.221	Na	Na	na
UPDRS-III score	15.9±9.3	21.2±11.3	25.0±6.5	4.760	2	0.01	0.09	0.008	0.403
	PD	PSP-P	PSP-RS	χ2	df	p			
Sex (Male, %)	84 (54.2%)	7 (63%)	6 (42.8%)	1.117	2	0.573	Na	Na	na

Data represent mean±SD; PD = PD; PSP-P = Progressive Supranuclear Palsy-Parkinsonism; PSP-RS = Progressive Supranuclear Palsy-Richardson syndrome; UPDRS-III = Unified PD Rating Scale - Part III; na = not applicable; PLSD = Fisher's Protected Least Significant Difference.

Alexithymia and anhedonia rating scales and diagnosis

The three groups differed significantly in the TAS-20 total, F1 and F2 scores. Both PSP-P and PSP-RS patients scored worse than PD ones at TAS-20 total and F1 subscale; only PSP-RS had significantly higher F2 score than PD group (Table 5.2.2).

Significant differences among PD, PSP-P and PSP-RS were found in the SHAPS scores: PSP-P and PSP-RS patients had significantly higher anhedonic symptoms than PD patients. As to neuropsychiatric diagnoses, alexithymia was more frequent in both PSP subtypes respect to PD patients (Table 5.2.2).

Table 5.2.2: Alexithymia and Anhedonia in patients with PD, PSP-P and PSP-RS.

Variables	PD (n=155)	PSP-P (n=11)	PSP-RS (n=14)	F	df	P	Post Hoc analysis		
							P PD vs. PSP-P	P PD vs. PSP-RS	P PSP-P vs. PSP-RS
TAS-20 total	46.2±11.7	55.2±18.1	59.2±11	8.790	2	0.0002*	0.0182*	0.0004*	0.4213
TAS-20 F1	12.2±5.8	16.4±7	17.6±11.1	5.823	2	0.0036*	0.0349*	0.0055*	0.6700
TAS-20 F2	13.4±5.9	16.4±7.6	18.7±7.1	5.235	2	0.0062*	0.1202	0.0038*	0.3486
TAS-20 F3	20.5±5.6	22.4±9.5	22.9±7.3	1.262	2	0.2856	na	na	na
SHAPS	0.439±0.8	1.2±1.5	1±1	5.464	2	0.005*	0.008*	0.0362*	0.6241
	PD	**PSP-P**	**PSP-RS**	**χ2**	**df**	**P**			
Alexithymia (% Y)	12.9%	54.5%	50%	21.027	2	<0.0001*	na	na	na
Anhedonia (% Y)	75%	12.5%	12.5%	1.094	2	0.5787	na	na	na

Data represent mean±SD. PD = PD; PSP-P = Progressive Supranuclear Palsy-Parkinsonism; PSP-RS = Progressive Supranuclear Palsy-Richardson syndrome; TAS-20 = Toronto Alexithymia Scale-20-item; F1 = TAS-20 difficulty identifying feelings; F2 = TAS-20 difficulty describing feelings; F3 = TAS-20 externally oriented thinking; na = not applicable; *Significant at p<0.05.

5.2.4 Discussion

To date, no data are available on alexithymia and anhedonia in patients with PSP-P and PSP-RS. Our results show clearly, for the first time, that PSP-P and PSP-RS patients are characterized by peculiar affective symptoms, already in the early stages of the diseases.

Indeed, PSP-P and PSP-RS show higher rate of alexithymia and alexithymic symptoms than PD. In particular, alexithymic severity and difficulty in identifying feelings may be

a specific aspect of PSP (PSP-P and PSP-RS), whereas the difficulty in describing feelings well characterizes only PSP-RS subtype in comparison to PD. In general, the presence of alexithymia distinguished PSP group from PD group, but not the two subtypes of PSP. Therefore, this finding supports the idea that alexithymic status and symptomatology could be a non-motor index of parkinsonism rather than PD in the early stage of onset of motor symptomatology. Similar results were obtained for anhedonia: anhedonia severity was higher in PSP-P and PSP-RS than in PD, despite no differences were found in the frequency of its diagnosis.

In general, our results translated in the daily life of PSP patients, meaning that these patients experience greater social, relational and behavioral difficulties than patients with PD. In fact, people with alexithymic status or symptomatology are unable to cognitively elaborate emotions or conceptualize them by mental imaging or words. Therefore, in PSP alexithymia, which includes deficient empathetic ability, could lead to great impairment of emotional processing and organizing that can seriously compromise communicative and interactive abilities of patients. This may have an impact on social intelligence, because the ability to understand emotions has a significant role in good social functioning.

The same result is product by anhedonia since, in a broader way, we can say that anhedonia is the inability to desire gratification. In fact, anhedonic patients experience an inadequate way of relating to the environment, which manifests itself with a

tendency to isolation. In other words, in PSP patients anhedonia can act not only on the psychological perception of pleasure to something, but also affects the willingness of patients leading to annihilation of any useful energy and interest to perform the most common and basic human activities.

This work adds further insights into the clinical variability between PSP and PD patients. In particular, PSP-P and PSP-RS represent two separate manifestations of PSP tau pathology [18]. In our previous study, we demonstrated that this assumption is reflected by neuropsychiatric and cognitive evaluations (see section 5.1). Now, our new results corroborate even more such an idea. In fact, we showed that alexithymia and anhedonia are common in both PSP subtypes and differentiate them from PD, which seems to be less affected from these phenomena. Moreover, a specific dimension of alexithymia, that is difficulty in describing feeling, seems to be more characterizing the PSP-RS. In particular, this group shows significant differences also in alexithymic F2 subscale (difficulty describing feelings) respect to PD. Accordingly to differences in regional burden of tau pathology observed in post-mortem pathological studies [17, 18] this could be due to more severe cortical atrophy and frontal lobe tau pathology in PSP-RS than PSP-P [27]. This latter justifies the increased difficulty in verbal fluency that we have found in PSP-RS patients (see section 5.1) and thus the difficulty in describing feelings.

Moreover, it is well known that patients with clinically established PSP exhibit distinct

patterns of atrophy, particularly affecting the frontal lobe and subcortical structures than PD [10, 23, 44, 47, 48], explaining our findings of greater impairment of affective and hedonic abilities in PSP patients, since alexithymia and anhedonia seem to be related to dysfunctions in these circuits. In particular, prefrontal, limbic and striatal abnormalities may significantly contribute to deficits in the effortful emotion regulatory process and in the emotion processing [40, 41, 49, 50].

Our study suffers from some limitations: first, our PSP patients were enrolled within Movement Disorders Outpatient Services, suggesting a predominant "motor" phenotype of the disease, and therefore possibly underestimating the prevalence and severity of affective impairment in the early PSP population; second the relative small sample size of PSP-P and PSP-RS patients advocates for further studies on larger series to confirm our findings.

In conclusion, PSP-P and PSP-RS exhibit worse alexithymic and anhedonic features than PD. Our results support the hypothesis that altered hedonic capacity and alexithymic symptoms mirror a basic neurophysiological dysfunction occurring precociously in PSP, therefore their identification could orient the diagnosis toward PSP cases; particularly difficulty in describing feelings could help to identify PSP-RS patients. Hence, our findings suggest that comprehensive psychiatric evaluations might be useful for diagnostic and therapeutic processes of PSP patients since the early stages of the disease.

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6. Advanced PD patients

6.1 Sociodemographic, neuropsychiatric and cognitive characteristics of pathological gambling and impulse control disorders NOS in PD

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Hereunder we report an excerpt of the study. Full-text of the related article can be found at:

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6.1.1 Background

The inability to resist an impulse, drive, or temptation to perform an act that is harmful to the person or others, defined as "impulse control disorder" (ICD), interferes with major areas of life functioning. Originally, ICD pertained to a variety of aberrant behaviors, including pathological gambling (PG). However, a distinction between PG and other variants of ICD (ICD-NOS), was initiated in the Diagnostic and Statistical Manual of Mental Disorders, IV Edition - Text Revision (DSM-IV-TR) [1] and defined in the 5th Edition of the DSM (DSM-5) that categorizes PG within the "Addiction and Related Disorders " Section [2].

ICDs have been identified in subjects suffering from PD [3, 4] with significantly higher prevalence than general population [5, 6]. Despite of consistent evidence for the association between ICDs and multiple demographic, clinical and therapeutic traits in PD [6-10], several issues remain unclear, particularly with respect to differences of neuropsychiatric and cognitive profile between PG and ICD-NOS.

The primary aim of the present study was twofold: first, to clarify the differences of neuropsychiatric profile of PD patients with PG as compared to those with ICD-NOS or without ICD (No-ICD) by means of a comprehensive approach based on both categorical and continuous classifications; second, to investigate the relationships between aberrant behaviors and specific cognitive functions in PD patients by using a complete neuropsychological battery.

We hypothesized that specific features and severity of neuropsychiatric profile could differentiate among PG, ICD-NOS and No-ICD. Conversely, we postulated the lack of difference of cognitive functions among the three conditions.

6.1.2. Methods

Participants and Study Design

The study was carried out on 155 PD patients aged between 35 and 80 years, diagnosed according to the criteria by Gelb et al. [11]. Participants were recruited consecutively during scheduled visits at the Outpatient Services for Movement Disorders of the “Fondazione Santa Lucia, IRCCS” and the “Sapienza Università di Roma - Ospedale Sant'Andrea”, between January 2011 and December 2012. Three neurologists with expertise in PD were in charge of diagnosis and selection of patients. The protocol was approved by the Ethical Committee of the “Fondazione Santa Lucia, IRCCS” and each subject signed an informed consent before enrollment. All patients were under stable dopaminergic therapy for at least 2 months before enrollment. Dopamine replacement therapy was calculated as daily levodopa equivalents. If the case of dopamine agonists, the following conversion table was applied: 100 mg levodopa = 1 mg pramipexole = 5 mg ropinirole = 5 mg rotigotine. Within each group, the number (and %) of subjects receiving antidepressant, benzodiazepines and/or antipsychotic therapy was calculated. Overall disease severity was staged according to

the modified H&Y scale [12]. The UPDRS-III was used to evaluate motor disability [13].

Exclusion criteria were as follows:

1. Co-morbidity with major medical illnesses.
2. Co-morbidity with primary neurological disorders such as stroke, Alzheimer's disease, head trauma with loss of consciousness, and others.
3. MMSE score <26.
4. Diagnosis of PD-dementia according to the clinical diagnostic criteria of the Movement Disorder Society [14]
5. Diagnosis of schizophrenia or bipolar disorder prior to the onset of motor symptoms.
6. CT or MRI evidence of significant focal cerebral abnormalities suggesting a secondary nature of parkinsonism.

All subjects were submitted to the SCID-P according to the DSM-IV-TR criteria[1]. A senior research psychiatrist made all psychiatric diagnoses. Symptoms of ICD were identified by means of the Questionnaire for Impulsive-Compulsive Disorders in PD (QUIP) [15] while the formal diagnosis of ICD was based on the DSM-IV-TR criteria. Patients were divided into 3 groups (i.e. PG, ICD-NOS and NoICD). If the case of multiple ICDs, the presence of PG drove inclusion of subject into the PG subgroup.

Neuropsychiatric and Cognitive Assessment

Four clinical neuropsychologists made all neuropsychiatric and neuropsychologic assessments. The neuropsychiatric evaluation included HDRS, HARS, SHAPS, ARS, PPRS and the Euro-QoL scale (ERS) [16] for measuring health-related quality of life.

All patients were submitted to a neuropsychologic evaluation including MMSE, RIR, RDR, PVF, SVF, CRO, DRO, WCST-SF and SWCT.

Statistical Analysis

Differences among the 3 groups were assessed by the chi-squared test for categorical variables and by a series of analyses of variance (ANOVAs) for continuous variables. Post-hoc comparisons were performed using Fisher's test for variables showing statistically significant differences on ANOVAs. For all tests, the level of significance was set at $p<0.05$.

6.1.3 Results

Demographic and Clinical Features

The demographic, neurological, and neuropsychiatric features of the study cohorts are summarized in Table 6.1.1. There were 21 (14%) PG subjects (pure PG=10; PG+ICD-NOS=11), 36 (23%) ICD-NOS subjects (hypersexuality=16; compulsive shopping=3; binge eating=10; hypersexuality+binge eating=4; hypersexuality+compulsive

shopping=1; compulsive shopping+binge eating=1; hypersexuality+compulsive shopping+binge eating=1) and 98 (63%) No-ICD subjects.

PG subjects were significantly younger than ICD-NOS and No-ICD ones. Moreover, ICD-NOS subjects were significantly younger than No-ICD ones. PG patients had younger age at symptom onset with respect to the other 2 groups. PG and ICD-NOS subjects had longer disease duration and were taking significantly higher total daily levodopa equivalents (both levodopa and dopamine agonists) than No-ICD ones. Conversely, there were no significant differences of prevalence of therapy with antidepressant, benzodiazepines or antipsychotics among the 3 groups.

There were no differences among the 3 groups as to sex, educational attainment, H&Y stage, UPDRS-III score and the prevalence of major depression, minor depression or generalized anxiety disorder.

Table 6.1.1: Demographic and Clinical Features of the Subjects Enrolled

	NoICD (n=98) Mean ± SD	PG (n=21) Mean ± SD	ICD-NOS (n=36) Mean ± SD	F	df	P	Post Hoc analysis		
							P PG vs. NoICD	P ICD-NOS vs. NoICD	P PG vs. ICD-NOS
Age (Years)	66±9	58±9	64±8	6.617	2	0.0018*	0.0004*	0.1813	0.0299*
Age at onset (Years)	61±9	51±8	57±10	12.23	2	<0.0001*	<0.0001*	0.0161*	0.0168*
Disease duration (Years)	5±3	8±5	7±4	6.768	2	0.0015*	0.0031*	0.0072*	0.4849
Education (Years)	10±4	10±4	11±4	0.638	2	0.5298	0.8194	0.3047	0.3532
H&Y score	1.8±0.5	2±0.5	1.9±0.8	1.769	2	0.1740	0.1183	0.1784	0.6779
UPDRS-III score	19±11.9	21.5±11.6	19.1±12.7	0.371	2	0.6909	0.3990	0.9787	0.4716
Daily Levodopa (mg)	251±279	487±625	388±278	5.139	2	0.0069*	0.0049*	0.0425*	0.2965
Daily DA Equivalents (mg)	166±197	307±275	316±374	5.838	2	0.0036*	0.0249*	0.0033*	0.8908
Daily Levodopa Equivalents (mg)	416±304	794±603	704±509	11.486	2	<0.0001*	0.0002*	0.0004*	0.4261
	n (%)	**n (%)**	**n (%)**	**χ2**		**P**			
Sex (F/M)	33/65	5/16	10/26	1.01	2	0.6034			
MDD	7 (7.1)	5 (23.8)	3 (8.3)	6.773	4	0.1484			
MIND	22 (22.4)	5 (23.8)	11 (30.6)						
NODEP	69 (70.4)	11 (52.4)	22 (61.1)						
GAD	12 (12.2)	3 (14.3)	7 (19.4)	1.121	2	0.5710			
Antidepressants	26 (26.5)	4 (19.1)	7 (19.4)	1.038	2	0.5950			
Benzodiazepines	12 (12.3)	3 (14.3)	7 (19.4)	1.121	2	0.5710			
Antipsychotics	4 (4.1)	2 (9.5)	3 (8.3)	1.484	2	0.4762			

SD=standard deviation; df=degrees of freedom; H&Y=Hoehn and Yahr scale; UPDRS-III= Unified PD Rating Scale – part III; MDD=Major Depressive Disorder; MIND=Minor Depressive Disorder; NODEP=No Depressive Disorder; GAD=Generalized Anxiety Disorder;*Statistically significant differences.

Neuropsychiatric Assessment

As shown in Table 6.1.2, PG subjects had significantly higher scores at the HDRS and HARS with respect to the other 2 groups. Moreover, PG subjects displayed a trend toward higher score at the SHAPS with respect to No-ICD ones.

Both PG and ICD-NOS subjects had significantly higher PPRS total score than No-ICD ones. Analysis of the different PPRS domains showed that both PG and ICD-NOS groups had significantly higher “sleep disturbances” and “sexual preoccupation” scores with respect to NoICD. Further, ICD-NOS patients had significantly higher “visual hallucination” and “paranoid ideation” PPRS domain scores, and significantly higher ERS score with respect to the other 2 groups. They also displayed a trend toward significance for higher PPRS “illusions” score. Finally, there were no differences among groups in the ARS and in the “confusion” domain of the PPRS.

Table 6.2.2: Psychopatologic Scores

	NoICD (n=98) Mean ± SD	PG (n=21) Mean ± SD	ICD-NOS (n=36) Mean ± SD	F	df	P	Post Hoc analysis		
							P PG vs. NoICD	P ICD-NOS vs. NoICD	P PG vs. ICD-NOS
HARS	8±5.7	13.6±6.4	8.9±7	7.128	2	0.0011*	0.0002*	0.4435	0.0065*
HDRS	7.2±5	11.2±5.6	8.4±4.6	5.499	2	0.0049*	0.0013*	0.2393	0.0435*
SHAPS	0.4±0.9	0.9±1.7	0.5±0.7	2.315	2	0.1022	0.0342*	0.8264	0.0883
ARS	8±6.3	8.9±5.3	7.1±6.3	0.570	2	0.5665	0.5324	0.4797	0.2950
PPRS Total	6.6±0.9	7.5±1.3	7.9±1.9	16.140	2	<0.0001*	0.0042*	<0.0001*	0.2013
PPRS Visual Hallucinations	1.1±0.2	1±0.2	1.2±0.4	3.181	2	0.0443*	0.8421	0.0171*	0.0613
PPRS Illusions	1±0.2	1±0.2	1.2±0.5	2.921	2	0.0569	0.8082	0.0176*	0.1382
PPRS Paranoid Ideation	1±0.1	1.1±0.3	1.2±0.4	5.259	2	0.0062*	0.1657	0.0019*	0.3072
PPRS Sleep Disturbances	1.3±0.6	1.7±0.6	1.7±0.8	7.051	2	0.0012*	0.0155*	0.0012*	0.8352
PPRS Confusion	1±0.1	1±0.2	1±0.2	0.254	2	0.7759	0.4801	0.8133	0.6519
PPRS Sexual Preoccupation	1.1±0.4	1.5±0.8	1.6±0.9	8.855	2	0.0002*	0.0089*	0.0002*	0.7244
ERS	7±1.1	7.5±1.5	7.7±1.7	3.694	2	0.0271*	0.1315	0.0124*	0.6397

SD=standard deviation; df=degrees of freedom; HARS=Hamilton Anxiety Rating Scale; HDRS=Hamilton Depression Rating Scale; SHaPS=Snaith-Hamilton Pleasure Scale; ARS=Apathy Rating Scale; PPRS=Parkinson Psychosis Rating Scale; ERS=Euro-QoL Scale; *Statistically significant differences.

Cognitive Assessment

Table 6.1.3 shows the lack of significant difference in any cognitive domain among the 3 groups. It is important to highlight that possibility of false negative results was excluded as all differences were far below the level of significance (p>0.1 for all comparisons).

Table 6.1.3: Neuropsychologic Scores

	NoICD (n=98) Mean ± SD	PG (n=21) Mean ± SD	ICD-NOS (n=36) Mean ± SD	F	df	P	Post Hoc analysis		
							P PG vs. NoICD	P ICD-NOS vs. NoICD	P PG vs. ICD-NOS
MMSE	28.5±1.3	28.8±1	28.8±1.3	1.181	2	0.3097	0.3120	0.1797	0.9456
RIR	35.8±10.2	39.3±10.2	38±10.5	1.336	2	0.2660	0.1602	0.2680	0.6556
RDR	7.2±3.3	8.6±2.2	7.8±3.4	1.907	2	0.1520	0.0633	0.3410	0.3385
CRO	28.3±4.1	28.3±5	29.2±4.1	0.325	2	0.7233	0.999	0.4328	0.5775
DRO	16.1±5.9	17.2±6.6	16.6±5.7	0.306	2	0.7371	0.4562	0.6984	0.7055
SWCT interference	45.3±17.3	44.5±20	44.4±15.4	0.076	2	0.9272	0.7974	0.7337	0.9867
SWCT word	16.5±4.2	15.2±3.4	15.7±3.4	0.913	2	0.4035	0.2673	0.3238	0.7857
SWCT color	22.5±6.3	22.8±7.3	20.7±3.6	1.346	2	0.2633	0.8493	0.1234	0.2073
SVF	18.8±5.8	17.7±4.6	18.7±5.4	0.334	2	0.7164	0.4157	0.8978	0.5340
PVF	31.9±10.6	30.1±10.1	30.2±9.5	0.506	2	0.6042	0.4764	0.3985	0.9807
WCST-SF categories	5.5±1.2	5.2±1.3	5.2±1.5	0.707	2	0.4948	0.3522	0.3578	0.8711
WCST-SF perseverative errors	2.9±4.3	4.3±4.8	3.4±7	0.722	2	0.4876	0.2466	0.5856	0.5291
WCST-SF non-perseverative errors	2.3±2.4	3.4±3.1	2.9±2.8	1.946	2	0.1464	0.0756	0.2317	0.4760

SD=standard deviation; df=degrees of freedom; MMSE=Mini Mental state Examination; RIR=Rey's 15-word test – Immediate Recall; RDR=Rey's 15-word test – Delayed Recall; CRO=Copy of the Rey-Osterrieth picture; DRO=Delayed Recall of the Rey-Osterrieth picture; SWCT=Stroop Word-Color Test; SVF=Semantic Verbal Fluency; PVF=Phonologic Verbal Fluency; WCST-SF=Wisconsin Card Sorting Test – short form.

6.1.4 Discussion

The present results demonstrate higher severity of depressive and anxious symptoms in PG patients with respect to the other groups (Table 6.1.2). This clarifies doubts raised from conflicting or inconclusive results in the literature [5, 17, 18] and allows to draw specific neuropsychiatric distinctions between PG and ICD-NOS. Our results also show more specific and severe psychotic symptoms in ICD-NOS subjects with respect to PG and No-ICD ones (Table 6.1.2). These findings may depend upon hypersensitivity of mesolimbic postsynaptic receptors to dopamine replacement therapy. Indeed, recent functional neuroimaging studies demonstrated reduction of dopamine re-uptake sites in the ventral striatum of PD patients with ICD [19, 20], therefore suggesting partial mesolimbic dopaminergic denervation.

The results of the present study also show the lack of relationship between ICD (both PG and ICD-NOS) and cognitive performances in undemented PD patients. These findings strongly argues against a causative link between specific cognitive dysfunction and ICD.

Our results confirm and extend previous reports on the association between impulsive/compulsive behaviors and some demographic, clinical or therapeutic features of PD [6-9, 17] (Table 6.1.1). Thus, daily dose of dopamine replacement therapy was significantly higher in PG and ICD-NOS as compared to No-ICD patients, although there were no differences between PG and ICD-NOS. These findings suggest

that excessive pharmacological stimulation of non-motor dopaminergic pathways may play a fundamental role in the development and maintenance of ICD in general, but not in determining the specific phenotype of aberrant behavior. This is consistent with an “overdosing” behavioral effect of dopaminergic drugs, and dopamine agonists in particular, on subcortical mesolimbic pathways in PD patients with ICDs [19].

Conversely, an age-dependent gradient of probability of developing different variants of ICD was found, younger subjects being particularly at risk for PG. This suggest that interaction between biological (age) and exogenous (dopaminergic drugs) factors may be relevant to determine the specific phenotype of ICD behavior in PD patients. Finally, the lack of relationships between ICD (any variant) and disease stage or severity of parkinsonian motor symptoms confirms previous reports, and indicate that PD patients should be monitored for ICD since the early clinical stages and independently from the rate of progression of motor symptoms.

The positive and negative results of the present study were strengthened by the use of rigorous psychiatric diagnostic criteria associated with specific neuropsychiatric and neuropsychologic scales. We acknowledge, however, that the moderate sample size did not allow specific analysis of the neuropsychiatric and cognitive features of the different behavioral variants of ICD-NOS and this have to be considered as a limitation of the present study.

In conclusion, the results of the present study clarify and extend previous knowledge

on the association between different phenotypic variants of ICD and multiple demographic, clinical and therapeutic domains in PD patients. In particular, we demonstrate different neuropsychiatric profiles between PG and ICD-NOS indicating that development of PG is coupled with significantly more severe depression and anxiety, and that development of impulsive/compulsive behaviors occurs independently from any selective impairment of cognitive function. This suggests that PD patients developing PG may represent a subset of subjects with distinct neurochemical and neuropathologic features.

6.2 Morphometric changes in the reward system of PD patients with impulse control disorders

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Hereunder we report an excerpt of the study. Full-text of the related article can be found at:

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6.2.1 Background

The mechanisms underlying the development of ICDs in PD are still poorly understood and their management can be challenging [21].

PET and fMRI studies have demonstrated mesocortical and limbic network dysfunction during valuation (risk-reward processing), motivation, decision-making and inhibitory control in PD patients with ICDs [22-27]. A SPECT connectivity analysis found specific functional disconnection between anterior cingulate cortex (ACC) and striatum in PD patients with pathological gambling [24]. These findings suggest that there is dysregulated reward processing in PD patients with ICDs including enhanced ventral striatum activity and poor cortical inhibitory control. Antecedent anatomical differences might underlie an increased vulnerability to ICDs [28]. If this is the case, structural MRI studies may help in clarifying why some patients are at greater risk for impulsivity. Alternatively, they may reflect the impact of non-physiological dopaminergic stimulation on the brain in sensitized individuals [29]. Recent data demonstrated reduced local gyrification index and grey matter atrophy in orbitofrontal cortex of PD patients with pathological gambling [30] and significant cortical thinning in fronto-striatal circuitry of PD patients with ICDs [31].

In this study we have used high-resolution structural 3-Tesla MRI and FreeSurfer automated reconstruction of cortical thickness (CTh) and subcortical nuclei, to investigate macrostructural alterations in mesocorticolimbic regions in medicated PD

patients with ICDs relative to PD patients without ICDs and healthy control participants. We hypothesized that the presence of ICDs would be associated with structural alterations in brain reward circuitry.

6.2.2 Methods

Participants and clinical characteristics

Thirty-six non-demented patients with PD who fulfilled the Queen Square Brain Bank criteria [11] were recruited from specialist movement disorders clinics at Imperial College Healthcare NHS Trust and King's Health Partners (Table 6.2.1).

Table 1. Demographic and Clinical features of the study cohort.

	HC	PD with ICDs	PD without ICDs
No	24	18	18
Age (years ± SD)	55.0 (±8.4)	56.6 (±9)	55.8 (±8)
Sex	20M / 4F	16 M / 2F	14 M / 4F
Age at onset (years ± SD)	–	46.2 (±10)	49.4 (±8)
Disease Duration[1](years ± SD)	–	10.4 (±4.8)	6.4 (±4.8)*
H&Y OFF[2](mean ±SD) [range]	–	2.3 (±0.5)[2-3]	1.9 (±0.5)[1-3]*
UPDRS-III OFF[3](mean ± SD) [range]	–	43 (±11) [17-71]	28 (±10) [7-47]**
MMSE (mean ±SD)	29.6 (±0.5)	29.3 (±1.2)	29.6 (±0.7)
Daily LED_{total}[4](mg ± SD)	–	789 (±370)	560 (±418)
Daily $LED_{levodopa}$ (mg ± SD)	–	644 (±411.5)	415 (±397.3)
Daily LED_{Dag}[5] (mg ± SD)	–	154 (±144)	124 (±125)
Patients treated with DAg (%)	–	12 (66.7%)	11(61.1%)

[1]From time of first appearance of PD motor symptoms;[2]H&Y: Hoehn and Yahr; [3]UPDRS-III: Unified PD Rating Scale Part-III. [4]LED: Levodopa Equivalent Dose; [5]DAg: dopamine agonist.*P<0.05; **P< 0.01

Eighteen of these satisfied the diagnostic criteria for one or more current ICDs according the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP) [15] and a formal diagnosis of ICD was made on the basis of the DSM-IV-TR following a semi-structured interview. Different type of ICDs including: pathological gambling, compulsive shopping, hypersexuality, binge eating, dopamine dysregulation syndrome, and problematic internet use were described by the patients and half had more than one ICD (Table 6.2.2).

Table 6.2.2. PD patients with ICDs.

Subject	Sex	Age	Type of ICDs	Daily $LED_{levodopa}$ (mg)	Daily LED_{Dag} (mg)
1	M	66	PG, CS	400	240
2	M	56	PG	1000	160
3	M	50	HS, PG, BE	0	200
4	M	67	PG	800	160
5	F	64	PG	1166	300
6	M	45	CS	1000	0
7	M	41	HS	1366	0
8	M	47	HS	400	0
9	M	60	CS, BE, PIU	600	300
10	M	59	PG	0	533
11	M	54	HS	260	240
12	M	54	HS, PG, BE, CS	867	80
13	M	66	HS, CS	533	0
14	F	56	HS, BE, CS	0	200
15	M	74	PG, DDS	866	160
16	M	51	HS,CS	1000	200
17	M	46	HS, BE	500	0
18	M	63	BE	833	0

PG=pathological gambling; CS=compulsive shopping; HS=hypersexuality; BE= binge eating; PIU=problematic internet use; DDS=dopamine dysregulation syndrome; LED: Levodopa Equivalent Dose; DAg: dopamine agonist

The other 18 PD patients had no history of ICDs. Twenty-four healthy controls (HC) matched for age and sex with no history of neurological or psychiatric disorders served as the control group.

Motor symptom severity was assessed with the UPDRS-III [13] and staged with H&Y [12]. Global cognitive status was assessed by MMSE in all participants. Dopamine replacement therapy was calculated as daily levodopa equivalents (LED) for each patient based on theoretical equivalence to levodopa [32].

The study was approved by the institutional review boards and the local research ethics committee. Written informed consent was obtained from all study participants in accordance with the Declaration of Helsinki.

Data acquisition and processing

All participants were scanned on a 3-Tesla Philips Intera whole-body MRI scanner. A T1-weighted three-dimensional magnetization-prepared rapid acquisition gradient-echo (MPRAGE; time echo: 4.6 ms; time repetition: 9.7ms; field of view: 240 ms; voxel size= 1 x1 x 1 mm) was acquired.

FreeSurfer's image analysis suite (version 5.3.0 http://surfer.nmr.mgh.harvard.edu) processing pipeline was used to derive measures of cortical thickness (CTh) and deep grey matter (GM) nuclei volume. This process consists of several stages, detailed elsewhere [33, 34].

We considered CTh measures of 10 selected cortical regions belonging to the mesocorticolimbic network and the following subcortical GM nuclei: caudate, putamen, globus pallidum, hippocampus, nucleus accumbens and amygdala (Table

6.2.3). All individual volumes were normalized for intracranial volume (ICV) automatically generated by FreeSurfer. Since no laterality was observed and for minimizing the number of comparisons, average hemispheric CTh and deep GM values were processed in the statistical analysis.

Statistical analysis

Statistical analyses were performed using Statistical Package for Social Science version 21.0. (SPSS, Inc. Chicago, IL, USA). For all variables, homogeneity and Gaussianity were tested with Bartlett and Kolmogorov-Smirnov tests. Demographic and clinical characteristics among groups were assessed by univariate analysis of variance with post-hoc Bonferroni's correction for continuous variables and by Chi-square test for categorical variables. Differences in clinical characteristics between PD patients with and without ICDs were analyzed using unpaired t-test and Chi-square test where appropriate. First, we run a one-way multivariate analysis of variance (MANOVA) with a single independent variable (i.e., group) with three levels to investigate differences in CTh and subcortical GM nuclei volume among groups. The omnibus level of significance for MANOVA was set at $P<0.05$. If the MANOVA was significant, we conducted a series of one-way ANOVAs, followed by Bonferroni's multiple-comparisons post-hoc tests ($P<0.05$ Bonferroni corrected), to compare means among groups. The level of significance was set at $P<0.05$ for the ANOVA comparative measurements. Additionally, even though age was not significantly different among

groups, the multivariate analysis was repeated adding age as covariate. Subsequently, in order to clarify our main research question, MRI data between the groups of PD with ICDs and PD without ICDs were compared for *F* and *P* values with multivariate analysis of co-variance (MANCOVA) using disease duration, and UPDRS-III score as covariates. If MANCOVA *P* values were significant ($P < 0.05$), we calculated a series of one-way ANOVAs, to compare means between-group. The level of significance was set at $p < 0.05$ for the ANOVA comparative measurements. Although we didn't find a significant difference between the groups of PD with ICDs and PD without ICDs in total daily LED, we run an additional MANCOVA between PD groups using total daily LED, disease duration and UPDRS-III as covariates. Additionally, even though age was not significantly different among groups, all the multivariate analysis were repeated adding age as covariate. We investigated differences in clinical and morphometrics data between PD patients with one ICDs and PD patients with multiple ICDs using MANOVA. Further, we ran linear regression analysis split by group (i.e., PD with ICDs; PD without ICDs) between total daily LED and those brain structures showing significant differences between PD groups by the results of MANCOVA. All data are presented as mean±SD, and the level α was set for all comparisons at $P<0.05$, corrected.

6.2.3 Results

Structural changes: comparisons to normality

We found significant differences in MRI measures among the three groups ($F_{2,57}$=2.62, *P*=0.001, η^2_p=0.494). Bonferroni's post-hoc tests showed volume loss in the nucleus accumbens of both PD patient groups: with ICDs (*P*=0.001) and PD patients without ICDs (*P*=0.001) when compared to healthy controls. PD patients with ICDs showed further significant atrophy in caudate (*P*=0.02), hippocampus (*P*=0.04) and amygdala (*P*=0.03) compared to healthy controls. Cortical thickness in rostral anterior cingulate and frontal pole was increased in PD patients with ICDs compared to the control group but the differences failed to reach corrected levels of statistical significance (Table 6.2.3). Covarying for age did not influence results.

Table 6.2.3: Cortical thickness and subcortical nuclei volume in PD patients with ICDs compared to the group of healthy controls.

	Healthy controls	PD with ICDs	*P* values*	% Change (PD ICD vs. HC)
Medial orbitofrontal cortex (mm; mean±SD)	2.21 (±0.04)	2.24 (±0.04)	>0.10	+1.4
Lateral orbitofrontal cortex (mm; mean±SD)	2.53 (±0.04)	2.52 (±0.05)	>0.10	-0.4
Frontal pole (mm; mean±SD)	2.56 (±0.05)	2.70 (±0.06)	>0.10	+5.5
Superior frontal cortex (mm; mean±SD)	2.63 (±0.04)	2.54 (±0.05)	>0.10	-3.4
Rostral middle frontal cortex (mm; mean±SD)	2.26 (±0.03)	2.29 (±0.04)	>0.10	+1.3
Parahippocampal cortex (mm; mean±SD)	2.64 (±0.06)	2.70 (±0.07)	>0.10	+2.3
Entorhinal cortex (mm; mean±SD)	3.15 (±0.09)	2.83 (±0.1)	>0.10	-10.2
Fusiform cortex (mm; mean±SD)	2.60 (±0.04)	2.43 (±0.05)	**0.04**	-6.5
Caudal anterior cingulate cortex (mm; mean±SD)	2.57 (±0.04)	2.60 (±0.05)	>0.10	+1.2
Rostral anterior cingulate cortex (mm; mean±SD)	2.76 (±0.04)	2.82 (±0.05)	>0.10	+2.2
Caudate (mean±SD)	2.27 (±0.05)	2.05 (±0.06)	**0.02**	-9.7
Putamen (mean±SD)	3.16 (±0.08)	2.98 (±0.09)	>0.10	-5.7
Globus pallidum (mean±SD)	0.94 (±0.02)	0.95 (±0.02)	>0.10	+1.1
Hippocampus (mean±SD)	2.77 (±0.06)	2.55 (±0.07)	**0.04**	-7.9
Nucleus accumbens (mean±SD)	0.55 (±0.03)	0.28 (±0.03)	**0.001**	-49.1
Amygdala (mean±SD)	1.03 (±0.03)	0.90 (±0.03)	**0.03**	-12.6

All the volumes are normalized by intracranial volume and multiplied by 1,000, thus dimensionless. **P* values are Bonferroni corrected.

Structural changes: comparisons within Parkinson's patients

Since PD patients with ICDs had significant longer disease duration (*P*=0.02) and higher UPDRS-III scores (*P*<0.01) than PD patients without ICDs we investigated differences in MRI measures between PD patients with and without ICDs using disease duration and UPDRS-III score as covariates ($F_{1,32}$=2.97, *P*=0.02, η^2_p =0.737). We found that Cth of rostral anterior cingulate cortex (*P*=0.002) and frontal pole (*P*=0.001) were thicker in PD patients with ICDs compared to the group of PD patients without ICDs (Fig. 6.2.1; Table 6.2.4).

Table 6.2.4: .Cortical thickness and subcortical nuclei volume in PD patients with ICDs compared to the group of PD patients without ICDs.

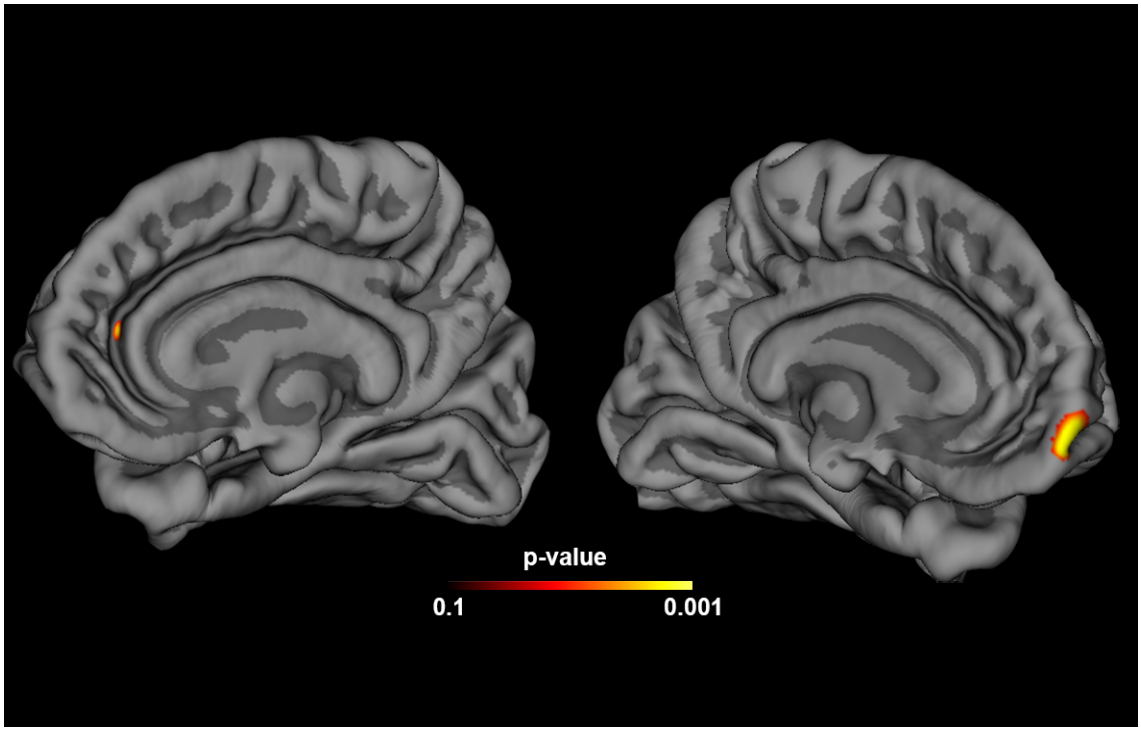
	PD without ICDs	PD with ICDs	*P* values*	% Change (PD ICD vs PD not ICD)
Medial orbitofrontal cortex (mm; mean±SD)	2.17 (±0.04)	2.24 (±0.04)	>0.10	+3.2
Lateral orbitofrontal cortex (mm; mean±SD)	2.43 (±0.05)	2.52 (±0.05)	>0.10	+3.7
Frontal pole (mm; mean±SD)	2.53 (±0.06)	2.70 (±0.06)	**0.001**	+6.7
Superior frontal cortex (mm; mean±SD)	2.51 (±0.05)	2.54 (±0.05)	>0.10	+1.2
Rostral middle frontal cortex (mm; mean±SD)	2.22 (±0.04)	2.29 (±0.04)	>0.10	+3.2
Parahippocampal cortex (mm; mean±SD)	2.53 (±0.07)	2.70 (±0.07)	>0.10	+6.7
Entorhinal cortex (mm; mean±SD)	2.92 (±0.1)	2.83 (±0.1)	>0.10	-3.1
Fusiform cortex (mm; mean±SD)	2.55 (±0.05)	2.43 (±0.05)	>0.10	-4.7
Caudal anterior cingulate cortex (mm; mean±SD)	2.44 (±0.05)	2.60 (±0.05)	>0.10	+6.6
Rostral anterior cingulate cortex (mm; mean±SD)	2.64 (±0.05)	2.82 (±0.05)	**0.002**	+6.8
Caudate (mean±SD)	2.10 (±0.06)	2.05 (±0.06)	>0.10	-2.4
Putamen (mean±SD)	3.11 (±0.09)	2.98 (±0.09)	>0.10	-4.2
Globus pallidum (mean±SD)	0.93 (±0.02)	0.95 (±0.02)	>0.10	+2.2
Hippocampus (mean±SD)	2.59 (±0.07)	2.55 (±0.07)	>0.10	-1.5
Nucleus accumbens (mean±SD)	0.32 (±0.03)	0.28 (±0.03)	>0.10	-12.5
Amygdala (mean±SD)	0.99 (±0.03)	0.90 (±0.03)	>0.10	-9.1

All the volumes are normalized by intracranial volume and multiplied by 1,000, thus dimensionless. **P* values corrected for disease duration and UPDRS-III.

The difference between the PD groups in total daily LED was not significant although it was considerable (Table 6.2.1), therefore we further calculated an additional MANCOVA including total daily LED, disease duration and UPDRS-III score as covariates ($F_{1,31}$=2.81, *P*=0.02, η^2_p=0.74). This analysis confirmed our previous findings. Cth of rostral anterior cingulate cortex (*P*=0.002) and frontal pole (*P*=0.001) were thicker in PD patients with ICDs compared to the group of PD patients without ICDs. Further, covarying for age did not influence results. The linear regression analyses split by group between Cth of rostral anterior cingulate cortex and total daily LED and Cth of frontal pole and total daily LED were not significant in both groups.

No significant differences were found in clinical and morphometric data between PD patients with one ICDs and PD patients with multiple ICDs.

Figure 6.2.1: Cortical thickness differences between PD patients with and without impulse control disorders.



For display purpose only, we have visualized our results using the whole brain GLM analysis provided by qdec. Given the aim of the figure, FDR and Montecarlo correction were not applied. The figure shows sagittal section of cortical areas with significant increased cortical thickness (i.e, rostral anterior cingulate, left side; frontal pole, right side) between PD patients with and without ICDs corrected for disease duration and UPDRS-III score. Difference maps are shown via a pseudo-color statistical overlay where black represents p 0.1 and yellow p 0.001. Red and yellow indicate thicker cortex in PD patients with ICDs with respect to patients without ICDs.

6.2.4 Discussion

Our findings demonstrate structural alterations in mesocortical and limbic reward-related areas including volume loss in ventral striatum, hippocampus and amygdala, and increased thickening of anterior cingulate (Brodmann Area-BA 32) and frontal pole (part of BA 10) cortices in PD patients with ICDs.

Indeed, we demonstrate significant volumetric differences in several regions within the

reward pathways, which reached corrected levels of statistical significance in PD ICD patients compared to healthy controls. We speculate that subcortical alterations in PD patients with ICDs may constitute a predisposing neural trait linked to impulsivity. Volumetric reductions in the accumbens and amygdala have previously been described in individuals at increased genetic risk for addiction [35] or with high levels of trait impulsivity [36] and a recent study of rats bred to be highly impulsive found volume reductions in the nucleus accumbens [26]. Alternatively, our findings might reflect the expression of secondary rearrangements of mesocorticolimbic system including derangement of deep gray matter nuclei and subsequent cortical remodeling. Indeed, a recent study in mice found that neural sensitization following repeated exposure to cocaine resulted in volume reductions in striatum and amygdala [29].

It is of interest that we found increased cortical thickness in specific frontal cortical areas, in particular rostral anterior cingulate and frontal polar cortex. While these increases in thickness may be related to a pre-existing neurobiological trait making subjects with thicker cortex more impulsive [37], they may also be secondary to neuroplastic adaptations associated with non-physiological dopaminergic stimulation occurring only in subjects with increased susceptibility to neural sensitization. Levodopa-induced increases in dorsal striatal dopamine release found in PD patients with ICDs are observed in PD patients with levodopa-induced dyskinesia (LIDs) [38]. Although LIDs and ICDs may occur under different clinical conditions, abnormal

behaviours in ICDs might parallel involuntary movements of LIDs as part of a pathological spectrum influenced by chronic non-physiological dopaminergic transmission and as results of similar form of neural sensitization operating on different brain systems [39]. Increased synaptic levels of dopamine and post-synaptic modifications such as changes in proteins and genes might determine an aberrant increase in the dendritic arborization, neuronal sprouting and neuropil and result in maladaptive synaptic plasticity [40-44]. In our study, we found increased thickness in medial frontal cortical areas involved in reward valuation and decision-making and we speculate that maladaptive synaptic plasticity occurring in these cortical areas could result in the behavioural manifestations of ICDs.

We also acknowledge the limitations of our study. The relative small sample size did not allow specific analysis of different variants of ICDs and a comprehensive neuropsychological and psychiatric evaluation was not performed on every patient. Moreover, we didn't perform a scale providing severity score for each ICDs and this has hampered correlation analysis between morphometric data and ICDs severity.

In conclusion, this study provides evidence of morphological abnormalities in PD patients with ICDs. We found increased cortical thickness in cortical regions involved in reward valuation and decision-making, as well as reduced volumes of subcortical components of reward circuitry. Our results suggest similarities between ICDs and LIDs as analogous side effects of non-physiologic chronic dopaminergic stimulation.

6.3 Unraveling predictors affecting compliance to MRI in Parkinson's disease

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Hereunder we report an excerpt of the study. Full-text of the related article can be found at:

https://www.ncbi.nlm.nih.gov/pubmed/26410743

6.3.1 Background

MRI is a sensitive, noninvasive and widely available technique for studying PD from both research and clinical perspective [45]. Numerous structural or functional MRI studies have attempted at clarifying cerebral correlates of motor and non-motor symptoms of PD [46]. In clinical setting, structural MRI allows recognition of secondary causes of parkinsonism and helps differentiating PD from atypical parkinsonisms [47]. Moreover, MRI may contribute at identifying potential biomarkers [48] for the early or pre-motor diagnosis of PD and monitoring effects of potentially neuroprotective strategies.

A number of factors (e.g. metal objects, clips, heart pacemaker, etc) may physically impede execution of MRI. Moreover, severity of motor and/or non-motor symptoms might reduce compliance to MRI by PD subjects.

This study was aimed at identifying predictors affecting compliance to MRI in PD, in order to define the extent to which patients enrolled in MRI studies are representative of the whole PD population, and to help precocious identification of subjects requiring particular preparation/premedication before undergoing the scan. We predicted that patients unable to perform MRI scan would show increased severity of neuropsychiatric and cognitive symptoms.

6.3.2 Methods

Two-hundred-thirty-six subjects, diagnosed as having PD according to international guidelines [11], were consecutively enrolled during scheduled visits at our Outpatient Services for Movement Disorders. They were all under stable and optimized dopaminergic therapy for at least 6 months, without need for booster doses of levodopa or dopamine agonists. Exclusion criteria were: vision or hearing non-compliance with procedures;

1. major not-stabilized medical illnesses;
2. history of alcoholism, drug dependence or abuse;
3. head trauma or other neurological disorders (other than PD);
4. psychiatric disorders (other than mood or anxiety disorder);
5. H&Y score > 3.

The study was approved by our Ethical Committee and each participant signed informed consent.

Demographic and neurological features were collected by trained neurologists at enrollment. Within 7 days from enrollment, all subjects underwent a SCID-P according to the DSM-IV-TR criteria. Patients were then submitted to a complete neuropsychiatric and cognitive assessment including: HARS, HDRS, PPRS, ERS, MMSE, RIR, RDR, CRO, DRO, SWCT- (interference time and word time), SVF, PVF and WCST-SF perseverative errors.

Acceptable inter-rater reliability was defined as k>0.80.

Following these evaluations, patients were submitted to an independent evaluation session to identify physical factors preventing execution of the MRI scan and to propose and furnish details on MRI procedure. Patients were then divided into 3 groups according to their compliance to MRI as expressed during the MRI evaluation session: 42 patients had physical incompatibility to MRI (PI), including metallic clips (n=22), severe kyphosis (n=10), heart pace-maker (n=3), severe dyskinesia (n=3), retinic or cervix uteri cerclages (n=2) and orthopedic implant (n=2); 51 patients refused (RR) to undergo the scan; 143 patients accepted to undergo and successfully performed MRI (SP).

Statistical Analysis

A series of univariate analyses of variance (ANOVAs) were used to assess differences in continuous variables (demographic, neurological, neuropsychiatric and neuropsychological) among groups. Bonferroni's post-hoc comparisons were performed for those variables showing statistically significant differences at ANOVAs. To minimize the likelihood of type I errors, ANOVAs were preceded by overall multivariate analysis of variance (MANOVA) using all neuropsychiatric and neuropsychological test scores as dependent variable. To identify predictors of compliance to MRI scan in the whole PD sample (i.e., SP+RR+PI), a logistic regression

analysis was carried out considering ability (i.e., SP) or inability (i.e., RR+PI) to undergo the scan as dependent variable and parameters showing significant ($p<0.05$) ANOVA differences among three groups as potential predictors.

6.3.3 Results

PI subject were significantly older, had higher UPRDRS-III score and received lower daily dopamine agonist doses that SP (Table 6.3.1).

Table 6.3.1. Demographic, clinical and neurological features of the study cohort

	PI (n=42) Mean ± SD	RR (n=51) Mean ± SD	SP (n=143) Mean ± SD	F	df	P	Post Hoc analysis		
							P PI vs. RR	P PI vs. SP	P RR vs. SP
Age (Years)	69.3±8.7	67.5±9.2	65.5±9.1	3.154	2	0.045*	0.997	0.053*	0.553
Age at onset (Years)	63.1±8.7	62.5±9.5	59.7±9.8	2.936	2	0.055	1.000	0.138	0.215
Disease duration (Years)	6.2±5.6	4.9±4.0	5.8±4.6	1.010	2	0.366	0.528	1.000	0.782
Education (Years)	10.2±5.0	9.7±4.4	10.3±4.3	0.424	2	0.655	1.000	1.000	1.000
H&Y score	2.0±0.7	1.7±0.6	1.8±0.5	2.689	2	0.070	0.070	0.221	0976
UPDRS-III score	23.6±11.9	18.3±13.1	18.0±10.9	3.914	2	0.021*	0.089	0.019*	1.000
Daily Levodopa (mg)	395±459	247±225	307±290	2.559	2	0.080	0.075	0.334	0.738
Daily Dopamine Agonist Equivalents (mg)	130±158	153±163	227±250	4.238	2	0.016*	1.000	0.039*	0.125
Daily Levodopa Equivalents (mg)	525±458	400±240	533±404	2.328	2	0.100	0.364	1.000	0.105

PI=physical incompatibility; RR=refused; SP=successfully performed; SD=standard deviation; df=degrees of freedom; H&Y=Hoehn and Yahr scale; UPDRS-III= Unified Parkinson's Disease Rating Scale – part III; *Statistically significant differences.

The MANOVAs carried out using neuropsychiatric and neuropsychological test scores as dependent variable indicated a significant global effect of groups (Wilks' lambda = 0.782; $F = 1.909$; $df = 30, 438$; p = 0.0031) on neuropsychiatric and neuropsychological performances.

Differences among the three PD groups in clinical characteristics are shown in Table

6.3.2. In particular, PI patients displayed significantly lower global cognition score and worse performances at several neuropsychological domains as compared to SP (Table 6.3.2). RR subjects had significantly higher anxiety score, as measured by the HARS, than SP. Both patient groups non undergoing MRI (PI and RR) had lower quality of life score than SP (Table 6.3.2).

Table 6.3.2: Neuropsychiatric and neuropsychological features of the study cohort

	PI (n=42) Mean ± SD	RR (n=51) Mean ± SD	SP (n=143) Mean ± SD	F	df	P	Post Hoc analysis		
							P PI vs. RR	P PI vs. SP	P RR vs. SP
HARS	9.3±7.4	10.8±6.0	7.3±4.8	8.089	2	0.000*	0.574	0.130	0.000*
HDRS	8.3±5.7	8.8±5.2	7.3±4.6	1.868	2	0.157	1.000	0.837	0.212
PPRS Total	6.8±1.0	7.0±1.2	6.8±1.2	0.502	2	0.606	1.000	1.000	1.000
ERS Total	7.4±1.8	7.3±1.6	7.1±1.4	0.687	2	0.504	1.000	0.936	1.000
MMSE	26.7±3.0	27.5±3.2	28.0±2.1	4.663	2	0.010*	0.465	0.010*	0.504
RIR	29.3±11.2	35.6±12.5	35.0±10.3	4.923	2	0.008*	0.019*	0.011*	1.000
RDR	5.6±3.4	6.8±3.6	7.2±3.4	3.577	2	0.030*	0.293	0.024*	1.000
CRO	25.1±7.5	26.3±7.6	27.9±5.8	3.466	2	0.033*	1.000	0.043*	0.404
DRO	12.4±6.4	14.3±6.0	15.1±6.2	3.205	2	0.042*	0.379	0.036*	1.000
SWCT interference time	57.7±34.6	47.9±17.7	49.0±23.3	2.316	2	0.101	0.174	0.140	1.000
SWCT word time	20.1±9.3	18.0±6.3	17.9±9.2	1.072	2	0.344	0.773	0.453	1.000
SVF	15.2±5.8	17.1±5.5	18.4±5.6	5.225	2	0.006*	0.304	0.005*	0.560
PVF	26.3±12.1	27.7±13.0	30.0±11.0	1.915	2	0.150	1.000	0.225	0.684
WCST-SF perseverative errors	7.7±9.5	6.8±9.9	4.4±6.3	3.651	2	0.027*	1.000	0.059	0.189

PI=physical incompatibility; RR=refused; SP=successfully performed; SD=standard deviation; df=degrees of freedom; HARS=Hamilton Anxiety Rating Scale; HDRS=Hamilton Depression Rating Scale; PPRS=Parkinson Psychosis Rating Scale; ERS=Euro-QoL Scale; ; MMSE=Mini Mental state Examination; RIR=Rey's 15-word test – Immediate Recall; RDR=Rey's 15-word test – Delayed Recall; CRO=Copy of the Rey-Osterrieth picture; DRO=Delayed Recall of the Rey-Osterrieth picture; SWCT=Stroop Word-Color Test; SVF=Semantic Verbal Fluency; PVF=Phonologic Verbal Fluency; WCST-SF=Wisconsin Card Sorting Test – short form.

*Statistically significant differences.

Based on the results of ANOVAs, we included as predictors in the logistic regression analysis the following variables: age; UPDRS-III score; daily dopamine agonist equivalent dose; HARS score; RIR score; CRO score; SVF score and WCST-SF perseverative errors. MMSE was not included being an index of global cognitive functioning. As to the memory domain, RDR and DRO scores were excluded because they showed lower statistical power compared with RIR score. Among potential predictors for lack of compliance with MRI in the whole PD sample (i.e., SP+RR+PI), only lower daily dopamine agonist equivalents (p=0.021) and higher score for anxiety (p=0.013) reached statistical significance.

6.3.4 Discussion

MRI gained high relevance in both research and clinical setting. PD patients may, however, suffer from several conditions preventing execution or completion of MRI scan, therefore research and clinical activities based on MRI findings may be affected by a significant selection bias. The purposes of the present study were to clarify to which extent PD patients undergoing MRI scan are representative of the whole PD population, and to guide clinicians in identifying variables that make patients incompliant to the exam. Our results show that several clinical, neuropsychological and neuropsychiatric features differentiate among PI, RR and SP patients. These findings suggest that research studies aimed at identifying cerebral alterations

associated with cognitive impairment in PD by MRI may suffer from biases of excluding more severely affected subjects. Indeed, RR patients displayed significantly higher severity of anxiety than SP. The present results support the hypothesis that brain MRI studies aimed at identifying the structural and functional alterations underpinning neuropsychiatric symptoms in PD cohorts (in particular anxiety) may exclude patients with more severe neuropsychiatric involvement.

Higher score for anxiety and lower daily doses of dopamine agonists were the unique significant predictors of inability to undergo MRI scan. These two factors may, indeed, be reciprocally related as dopamine agonists may exert therapeutic efficacy on symptoms of anxiety in PD patients [50].

In conclusion, the present results contribute defining motor and non-motor features of compliance to closed bore MRI by PD patients and provide valuable aid for setting and interpreting structural and functional MRI research studies in PD. Moreover, the identification of predictors of noncompliance to MRI may help clinicians to tailor psychological and/or pharmacological strategies helping patients to complete the exam.

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7. Conclusions

The prevalence of PD and thus the burden of associated neuropsychiatric and cognitive symptoms will increase in future years due to blatant trends in the age-structure of populations. Rising age in the general population often equates to an increase in co-morbidities and associated polypharmacy. Therefore, the detection and, if possible, prevention, of neuropsychiatric and cognitive symptoms associated with PD is of highest importance for future generations in terms of healthcare costs, social care and prevention of morbidity and mortality. Indeed, neuropsychiatric and cognitive assessments hence should be included in the routine evaluation of patients with PD in order to allow effective management of the patients. In turn, this approach can provide the patients and their families with adequate information enabling them to formulate a proper planning of their own future needs.

Following this integrative need, a clinician taking care of a patient suffering from PD does not have to treat motor symptoms alone, which belong to the field of neurology, but he also has do diagnose and treat affective or cognitive symptoms, which belong to the field of psychiatry. This approach attempts to overcome the paradoxical situation in the contemporary relationship between neurology and psychiatry. We strongly believe that PD may be regarded as a paradigmatic example of neuropsychiatric disease in a current gestalt and as an attractive model where the boundaries between neurology and psychiatry melt away because of the overlapping

of shared symptoms. Indeed, the motor action cannot be observed separated from affect/emotion and cognition because of the mutually overlapping systems, enabling the motor action to influence affect/emotion and cognition directly, and reverse. Neuropsychiatric-cognitive and motor alterations in PD should be no longer explained separately and independently but regarded as two expressions of a uniform dynamic-functional structure. It is the alteration of this structure, and not of the two different symptom complexes as two different phenomena, that has to be explained.

The conceptualization and understanding of PD symptoms by the integration of neurological and psychiatric knowledge is the leading thread of this research.

The studies discussed above described the contribution of neuropsychiatric and cognitive assessment in different scenarios and in different stages of PD.

In particular, our results here presented showed that:

- In untreated PD patients, the body side of onset of motor symptoms does not influence the pattern or severity of neuropsychiatric and cognitive abnormalities. Nor motor subtypes are associated with a specific cognitive and neuropsychiatric profile. These results support the idea that a possible cognitive-affective differentiation emerges only with the progression of the disease and potentially with its interaction with DRT.
- In early PD patients, whithin 24 months from the onset of motor symptoms, comprehensive cognitive and psychiatric evaluations might be useful and cost-

effective contributors to the diagnostic work-up of patients with progressive parkinsonism. Indeed, verbal fluency impairment and apathy diagnosis are more supportive of diagnosis of PSP-RS and PSP-P respectively, rather than PD. Further, difficulty in describing feelings could help to identify PSP-RS patients.

- In advanced PD patients, when the full picture is often complicated by interaction with DRT, neuropsychiatric and cognitive assessments are crucial in identifying subset of fragile patients. Indeed, we demonstrate different neuropsychiatric profiles between PG and ICD-NOS indicating that development of PG is linked with significantly more severe depression and anxiety, and that development of impulsive/compulsive behaviors occurs independently from any selective impairment of cognitive function. To shed more light into ICD issue, in a structural MRI study, we demonstrated increased cortical thickness in cortical regions involved in reward valuation and decision-making, as well as reduced volumes of subcortical components of reward circuitry in PD patients with ICDs. Finally, defining motor and non-motor features of compliance to closed bore MRI by PD patients, our results advice clinicians to tailor psychological and/or pharmacological strategies helping patients to complete the exam and investigators to set and interpret MRI research studies.

The results of the current research provide a valuable support in understanding the fruitfulness of neuropsychiatric and cognitive symptoms assessment in the diverse stages of PD. Nonetheless, yet more efforts have to be made. Certainly, future directions urge to include longitudinal evaluation and larger study cohorts to confirm the present findings.

8. Ancillary Research

8.1 Phosphorylated α-synuclein immunoreactivity in nerve fibers from minor salivary glands in Parkinson's disease

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8.1.2 Methods

Seven patients diagnosed with PD according to the UKPDBB criteria [1] with disease duration >3 years and sustained response to dopaminergic therapy, and 7 healthy volunteers were recruited. They all signed informed consent. Exclusion criteria for both groups were: *i*. MMSE score <26; *ii*. Bleeding diathesis; *iii*. Anticoagulant therapy; *iv*. Systemic disorders contraindicating biopsy; *v*. Known or suspected salivary gland pathology. Under local anesthesia with xylocaine, minor salivary gland biopsy was performed and tissue was immediately frozen in paraformaldehyde. There was no report of adverse event.

Tissue sections were cut on the microtome, mounted on electrostatically charged glass slides, deparaffinized and rehydrated, then treated with either citrate buffer (0.01 mol/L, pH 6) in microwave (750 W) (for α-synuclein) or proteinase K in phosphate buffered saline pH 7.0 (37°C, 20 minutes) (for Ser129-phosphorylated-α-synuclein). Three consecutive tissue sections were obtained at 3 different levels from each biopsy. For each triplicate, sections were incubated with either mouse monoclonal anti-α-synuclein (code LB509, Zymed Laboratories, Invitrogen, 1:200, 1h, RT), mouse monoclonal anti-Ser129-phosphorylated-α-synuclein (code pSyn#64, Wako, Japan, 1:1000, 1h, RT), or rabbit policlonal anti-S100 (code Z311, Denmark, 1:300, 1h, RT), respectively. The reaction was amplified with LSAB2+System-HRP (Dako, CA, USA). Positive immunoreaction was identified after incubation with 3,3'-diaminobenzidine

(DAB) and counterstaining with Mayer hematoxylin. Negative controls were obtained omitting the primary antibodies.

Immunostaining was quantified on 5-Mp (24-bit color depth) images (400x magnification) from all sections of each salivary gland (mean area 13,888,121.35 μm^2) (ImageJ software, NIH, USA). For each sample, immunostaining was expressed as the mean positive area normalized to the total area of the examined section, and expressed as the ratio between areas. Values for α-synuclein and Ser129-phosphorylated-α-synuclein were also normalized to the S100 value indicative of the presence of nerve fibers in the examined gland and expressed as the ratio between areas. Data were expressed as means±SEM. The results were analyzed with the Student's t-test, threshold for significance being set at $p<0.025$.

8.1.3 Results

The ratio of nerve fibers immunoreactive to α-synuclein (α-synuclein$^+$/S100$^+$ ratio) was not significantly decreased in PD patients compared with healthy subjects (0.039±0.046 vs. 0.149±0.030; $p>0.025$).

Conversely, Ser129-phosphorylated-α-synuclein immunoreactive nerve fibers (Ser129-phosphorylated-α-synuclein$^+$/S100$^+$) were identified in 5/7 PD cases (0.004±0.006) but never in control subjects ($p<0.025$) (Fig 8.1). Immunostaining was found also in the cytoplasm of some acini and ductule cells from subjects belonging to

both groups; rarely, secretory material within ductules was also stained.

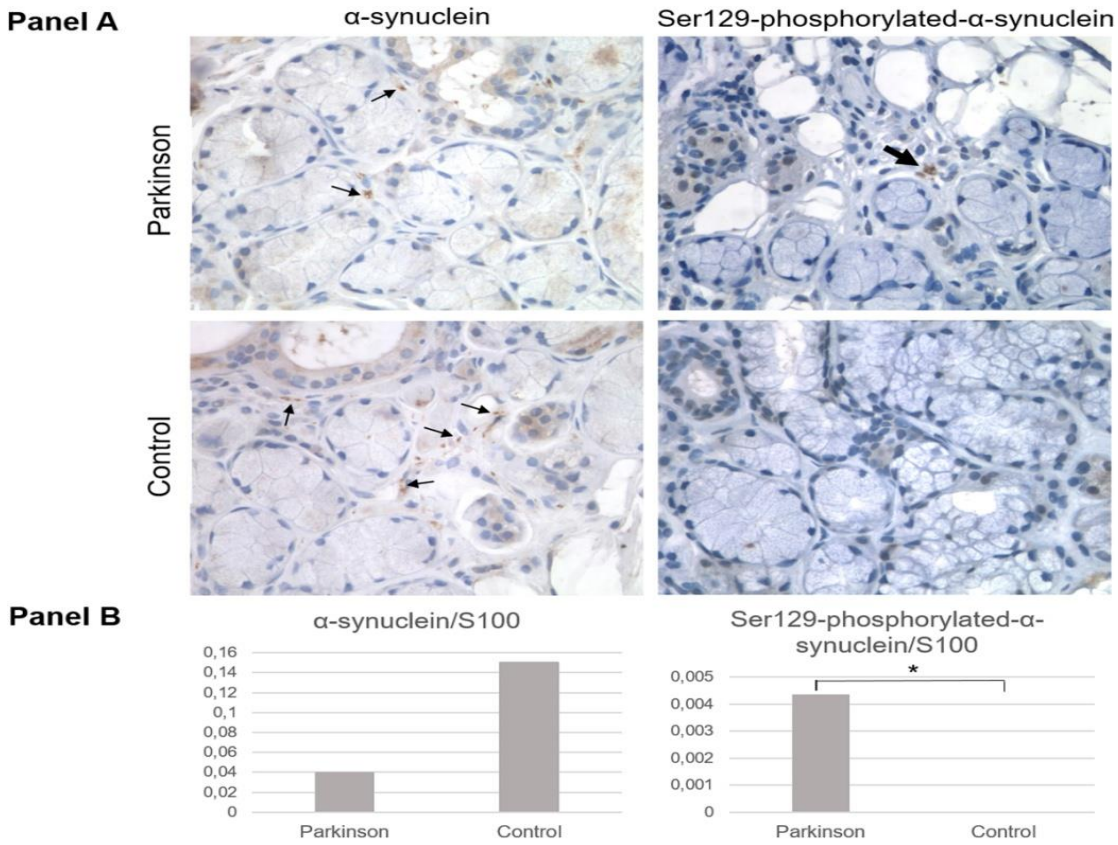

Fig 8.1. Panel A. Representative photomicrographs (original magnification x40) of salivary gland tissue showing very thin nerve fibers immunostained with alpha synuclein (thin arrow) and Ser129-phosphorylated-a-synuclein (thick arrow) in PD patients and healthy subjects. Panel B. Immunostaining quantification of alpha synuclein and Ser129-phosphorylated-a-synuclein in PD and healthy subjects. The graphics show immunostaining for Ser129-phosphorylated-a-synuclein/S100 (*p < 0.025) only in in PD together with reduced immunostaining for a-synuclein/S100 compared to healthy subjects.

8.1.4 Discussion

Accuracy of clinical diagnosis of PD ranges between 50 and 90%, prolonged clinical observation and response to dopaminergic therapy being the most reliable markers [1]. Identification of biomarkers supporting PD diagnosis early along disease course is,

therefore, of great interest. Interestingly, Ser-129-phosphorylated-α-synuclein is a biochemical hallmark of PD and other Lewy body disorders, not detectable by immunohistochemistry in normal neural tissue [3]. Nerve fibers immunoreactive to Ser129-phopshorylated-α-synuclein have been reported previously in submandibular gland biopsies from PD patients [2,3]. Despite the potential advantage of being a less invasive procedure, minor salivary gland biopsy failed to provide sufficient sensitivity in previous studies [3,4].

Differently from those previous reports [3,4], we applied semi-quantitative analysis for identifying immunostaining with monoclonal anti-Ser129-phopshorylated-α-synuclein antibody in nerve fibers from minor salivary gland biopsies in PD patients but not healthy controls. This was accompanied by reduced immunostaining for α-synuclein in nerve fibers from PD patients, as if abnormal phosphorylation of α-synuclein would occur in peripheral nerve fibers in the minor salivary glands in the majority of PD cases.

Finally, the immunostaining for α-synuclein in acini and ductule cells and the identification of immunostaining in secretory material within ductules may be of interest for the recent report of abnormal salivary total and oligomeric α-synuclein in PD [5].

In conclusion, the results of this pilot study suggest that semi-quantitative measurement of immunoreactivity to α-synuclein and Ser129-phosphorylated-α-synuclein may discriminate PD patients from healthy controls. If confirmed on larger series, this approach might

provide a useful, poorly invasive, support to the clinical diagnosis of PD.

8.1.5 References

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8.2 The PD-Manager Project: m-health platform for Parkinson's disease management. Project overview

http://www.parkinson-manager.eu/

"PD-Manager: mHealth platform for Parkinson's disease" is an international project Co-funded by the European Union's Horizon 2020 Framework Programme for Research and Innovation under Grant Agreement No 643706.

The study will be coordinated by the Jožef Stefan Institute in Ljubljana while the technical aspects will be supervised by the Biomedical Engineering Department of the University of Ioannina. The clinical partners are the IRCCS San Camillo Hospital of Venice, IRCCS Santa Lucia in Rome (Neuropsychiatry Laboratory, Department of Clinical and Behavioral Neurology), the Neurology Clinic of the University Ioannina

(Greece) and the rehabilitation Centre University of Ljubljana (Slovenia).

After the definition of user needs under the coordination of the psychology unit of the University of Surrey, the project will involve in the pilot phase, 30 patients and, at the end of 2016, it will become one of the largest multi-centre studies involving a total of 230 patients across four European centres. During the stages of advancement, updates will be provided with live demonstrations of the achievements, to all the countries involved utilising the power of the web. Furthermore, the technologies that will result will be made available to all. The project partners are please to have the support of the European Parkinson Disease Association (EPDA) who will help in the trans-national dissemination of results.

The PD_manager project aims to:

- Propose a set of unobtrusive, simple-in-use, co-operative, mobile devices that will be used for symptoms monitoring and collection of adherence data (smartphone, sensor insole, wristband with several sensors for acceleration, heart rate, etc.).
- Model the behaviors of intended users of PD_manager (patients, caregivers, neurologists and other health-care providers).
- Educate patients, caregivers and healthcare providers with the focus on occupational and speech therapies

A smart watch, an insole to measure gait and balance, an electronic pillbox and a set of applications for smartphone, will enable a medical team to monitor and assess the motor, emotional and cognitive state of people with PD during their daily life at home.

With the support of a powerful server and online data collection system, it will be possible to provide each patient the specific therapeutic changes necessary to ensure the best treatment and develop rehabilitation focused home-care system that will improve quality of life and reduce the risk of complications including falls.

The project, started in January 2015, is now in its final phase and we are gathering data from 230 patients.

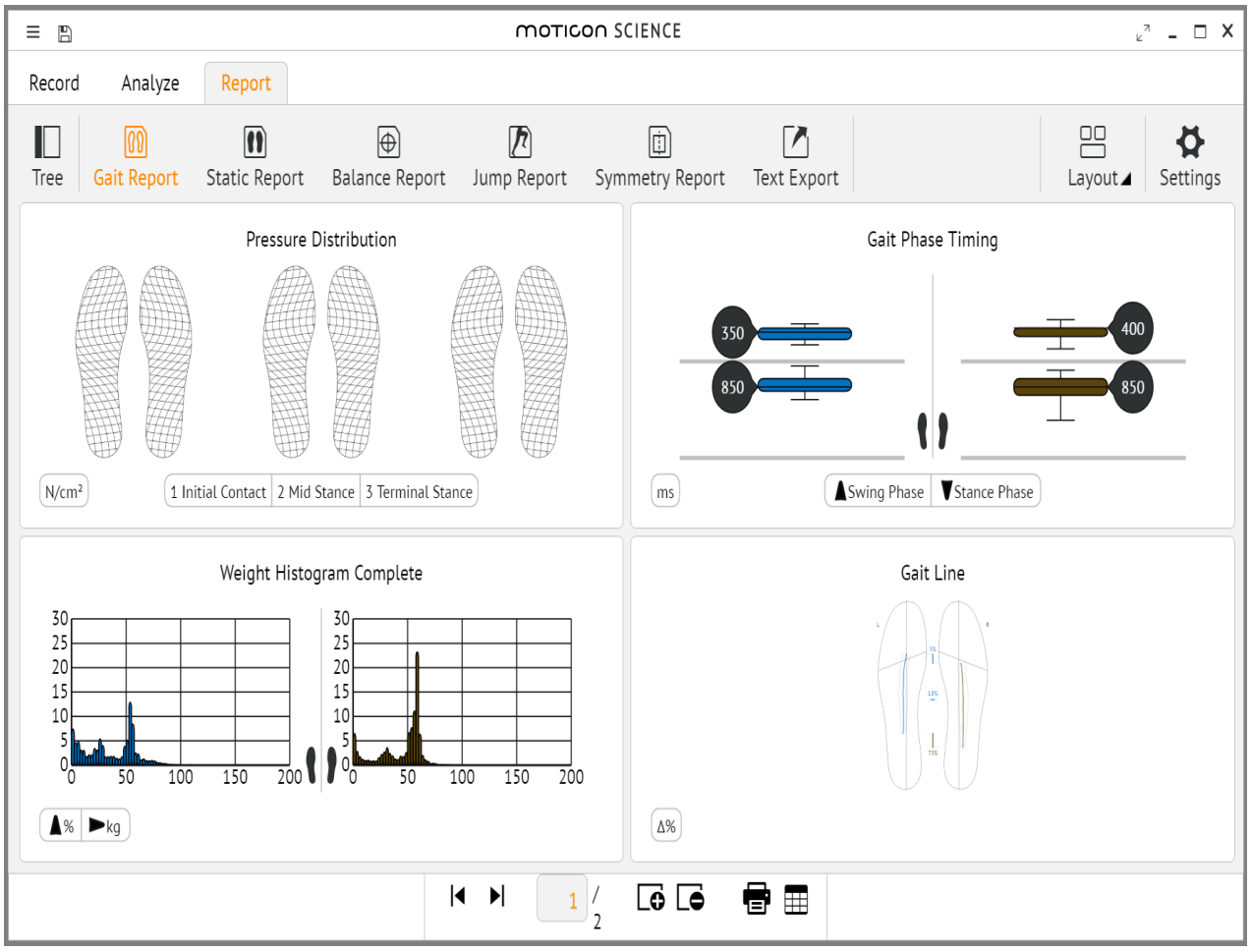

Fig.8.2: Dashboard of the insole mesaurements

8.3 The PICASO Project: A Personalized Integrated Care Approach for Service Organizations and Care Models for Patients with Multi-Morbidity and Chronic Conditions. Project overview

http://www.picaso-project.eu/

The "Personalized Integrated Care Approach for Service Organizations and Care Models for Patients with Multi-Morbidity and Chronic Conditions.-PICASO project" is an international project Co-funded by the European Union's Horizon 2020 Framework Programme for Research and Innovation under Grant Agreement No 689209.

The PICASO project aims to develop an ICT platform which will support the coordination of care plans across different sectors for people diagnosed with co-occurring chronic diseases. The PICASO project addresses three main challenges in Europe's healthcare systems:

- managing multi-morbidities;
- coordinating care and treatment across organizational silos
- adapting ehealth solutions to existing care models and plans.

The technologies will be trialed in a German and an Italian setting. In Germany, the University Hospital of Düsseldorf will involve their patients diagnosed with Rheumatoid Arthritis. In Italy, the University Hospital of Tor Vergata in Rome, in collaboration with Neuropsychiatry Laboratory Department of Clinical and Behavioral Neurology of IRCCS Santa Lucia Foundation, engage patients with PD. Both patient groups have Cardiovascular Diseases and/or other co-morbidities.

The technology

The PICASO platform is a service oriented, ICT based integration platform based on dynamic and personalized orchestration of care services. The method for sharing patient information between all relevant formal and informal care providers is by using a unique, trust federated solution, thereby overcoming the problem of data privacy in cloud based health systems. . Each patient will be monitored at home with a smart wristband collecting data about heart rate, sleep quality and daily steps covered. Futher, therapy reminder tool and blood pressure measurement instrument is provided.

The platform contains an Integrated Care Platform, a Data Management Platform and

a Multi-Morbidity Decision Tool.

The PICASO Integrated Care Platform:

- is an integration platform for sharing a patient's complete care pathways across multi-actor care spaces.The Platform, with appropriate tools such as risk prediction models for the interpretation of patients' immediate and future health status, the ability to dynamically adjust the content and management of the delivered care services, is so always adapted to the patient's personal health status and ability.
- Contains a robust, privacy compliant, cloud based Resource Management system that can perform acquisition of physiological and behavioural data in non-clinically controlled care spaces, taking into account the variability in the population to provide carers with realistic situational awareness.
- Creates a new approach to integrated care based on the concepts of dynamic service narratives that define the workflow (content and management of care services) to be launched and orchestrated across the relevant care spaces.
- Provides decision support for multi-actor interaction and enables patients and relatives to become active participants.

The PICASO Data Management Platform:

- Provides role-based access for carers to distribute shared data and exchange of knowledge about the patient's status in an intuitive collaborative platform.
- Provides a framework for secure, privacy compliant, and role-based information sharing through a common view of data allowing carers to control and share patient information and exchange knowledge across care networks using intuitive, interactive ad-hoc information search.

The PICASO Multi-Morbidity Decision Support Tool:

- Contains a decision support methodology for analyzing conflicts, constraints and limitations from single-morbidity care plans and patient/physician/therapist preferences applied to patients with comorbidities and multi-morbidity conditions by using the concept of constraint satisfaction problem, to allow the cares to define new care programs for the management of co-morbidities in community and home care settings.
- Forms the basis for new training programs for the care workforce, new organizational models and new ways of exchanging medical information to improve the coordination of multi-morbidity care management across silos.

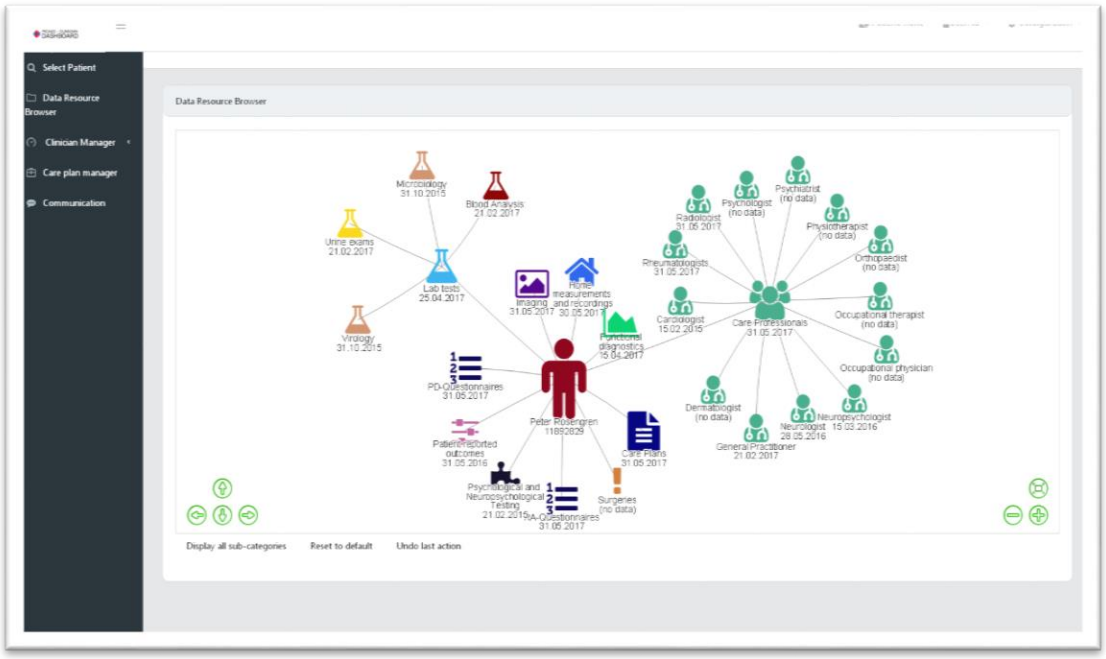

Fig 8.3 Clinician Dashboard showing the integrated health care net.

Fig 8.4 Clinician Dashboard showing the collected mesaurments.

9. Related Publications

9.1 Papers

1 **Pellicano C**, Assogna F, Cravello L, Langella R, Caltagirone C, Spalletta G, Pontieri FE. On the relationship between side of onset and cognition in Parkinson disease: Response from the Authors. Parkinsonism Relat Disord. 2015 Dec;21(12):1481-2

2 **Pellicano C**, Assogna F, Cravello L, Langella R, Caltagirone C, Spalletta G, Pontieri FE. Neuropsychiatric and cognitive symptoms and body side of onset of parkinsonism in unmedicated Parkinson's disease patients. Parkinsonism Relat Disord. 2015 Sep;21:1096-100

3 **Pellicano C**, Assogna F, Cellupica N, Piras F, Pierantozzi M, Stefani A, Mercuri B, Caltagirone C, Pontieri FE and Spalletta G. Neuropsychiatric and Neuropsychological profile of early Progressive Supranuclear Palsy and Parkinson's Disease. Accepted at Parkinsonism Relat Disord. 10.1016/j.parkreldis.2017.10.002

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11 Assogna F, Cravello L, **Pellicano C**, Savini C, Pierantozzi M, Mercuri B, Pontieri FE, Caltagirone C, Spalletta G, Stefani A. Cognitive and neuropsychiatric profile of tremor dominant and akinetic-rigid motor subtypes of newly diagnosed drug naïve Parkinson's disease patients. In preparation.

12 Assogna F, **Pellicano C**, Cravello C, Cellupica N, Savini C, Pierantozzi M,Stefani A, Mercuri B, Caltagirone C, Pontieri FE, Spalletta G. Affective impairment and emotional tone of early Richardson's syndrome and Progressive Supranuclear Palsy-parkinsonism: the role of Alexithymia and Anhedonia. In preparation.

9.2 Poster presentations

1. Wilson H, Niccolini F; **Pellicano C**; Politis M. Staging and clinical correlates of cortical thinning in Parkinson's disease. 20th International Congress of Parkinon's Disease and Movement Disorders, June 19-23, 2016, Berlin,

Germany

2. **Pellicano C**, Assogna F, Cellupica N, Pierantozzi, M, Stefani A, Cerroni R, Mercuri B, Caltagirone C, Pontieri FE, Spalletta G, "Predittori neuropsichiatrici e cognitivi della diagnosi precoce di Paralisi Sopranucleare Progressiva". 3rd Congresso dell'Accademia LIMPE-DISMOV, May 19-20, 2017, Verona, Italy
3. **Pellicano C**, Assogna F, Cellupica N, Pierantozzi, M, Stefani A, Cerroni R, Mercuri B, Caltagirone C, Pontieri FE, Spalletta G, "Neuropsychiatric and Cognitive Predictors of Early Diagnosis of Progressive Supranuclear Palsy". 21st International Congress of Parkinson's Disease and Movement Disorders, June 4-8, 2017, Vancouver, Canada