The neuropsychiatric profile of Parkinson's disease subjects with and without mild cognitive impairment

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Abstract Neuropsychiatric symptoms (NPS) are common clinical features of Parkinson's disease (PD). However, NPS profiles in PD subjects with mild cognitive impairment (MCI) have scarcely been investigated. We aimed to describe the NPS profiles of non-demented PD subjects with and without MCI. A total of 410 non-demented PD subjects were included. Of these, 164 were cognitively normal PD subjects (PD-cn), 142 PD had amnestic MCI (PD-aMCI), and 104 had PD with non-amnestic MCI (PD-naMCI). NPS were evaluated in accordance with the Neuropsychiatric Inventory (NPI). PD-aMCI subjects revealed the highest NPS burden, followed by PD-naMCI and then PD-cn. Overall, the most common NPS in PD-MCI were in order: depression, sleep disturbance, anxiety and apathy. Irritability was significantly associated with PD-aMCI and PD-naMCI. Prospective studies are required to evaluate the significance, clinical correlates and prognostic role of NPS in subject with PD-MCI.

Keywords Parkinson's disease · Cognitive impairment · Neuropsychiatric symptoms · Epidemiology

Introduction

In recent years, mild cognitive impairment (MCI)—a nosological entity which has been proposed as an intermediate state between normal aging and dementia (Mariani et al. 2007)—has also been applied to non-demented subjects with Parkinson's disease (PD) (Litvan et al. 2011), and formal diagnostic criteria for PD-MCI have been recently proposed (Litvan et al. 2012). MCI is common in PD, being associated with increasing age, disease duration, and disease severity (Litvan et al. 2011). However, to date the clinical correlates, risk and prognostic factors of PD-MCI are relatively unknown.

Neuropsychiatric symptoms (NPS), including sleep disturbance, depression, anxiety, fatigue, apathy and hallucinations (Aarsland et al. 2009), are frequent clinical features of PD. NPS in PD are highly prevalent, affecting patients' quality of life, prognosis and treatment, particularly in subjects with PD and dementia (Aarsland et al. 2009). As is the case with dementia and PD, NPS have not been included in the concept of PD-MCI (Litvan et al. 2012), and only recent research has described the neuropsychiatric features of the condition in a convenience sample of 48 UK subjects with PD-MCI, consecutively drawn from community clinics (Leroi et al. 2012).

The aim of this study is to describe the neuropsychiatric profile in non-demented PD subjects with and without MCI, selected from a large hospital-based sample, subsequently evaluating specific NPS in use in differentiating PD-MCI versus PD subjects without cognitive impairment.

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Materials and methods

Participants

Subjects with PD were consecutively identified from the Outpatient Movement Disorders Clinic of the Neurology and Cognitive Disorders Unit, University Hospital,

Palermo, Italy over an 11-year period (2001–2011). These PD subjects belong to a larger, prospective, hospital-based study, which was carried out from 2001 to present in our neurological unit and clinics, and which focused on normal and pathological aging (Cognitive Impairment through Aging, CogItA) (Monastero et al. 2012). All patients underwent an extensive physical, neurological, and neuropsychological examination, laboratory testing and computed tomography or magnetic resonance imaging. From a total of over 500 subjects with PD seen over the 11-year period, 410 non-demented PD subjects with mild-moderate disease were included (i.e., Hoehn and Yahr scale, stage I-III) (Hoehn and Yahr 1967). PD was diagnosed according to the UK PD Society Brain Bank criteria (Hughes et al. 1993). Specifically, we evaluated the prevalence of rigidity, resting tremor and postural instability in PD subjects to assess whether specific cardinal signs of PD (apart from bradykinesia) may affect specific NPS expression in PD. The PD motor assessment included the Unified Parkinson's Disease Rating Scale-motor examination (UPDRS-ME) (Fahn et al. 1987). To evaluate the overall burden of dopaminergic drugs for each PD subject, we calculated the total daily levodopa equivalent dose (LED), obtained by adding together the LED for each antiparkinsonian drug (Tomlinson et al. 2010). Furthermore, we evaluated the prevalence of antipsychotic (ATC code: N05A), anxiolytic (ATC code: N05B), and antidepressant drugs (ATC code: N06A) (World Health Organization 2011) in PD subjects to evaluate the effect of psychotropic drug use on the association between PD and specific NPS. The exclusion criteria were: a diagnosis of a severe systemic disorder; psychosis; a history of significant head injury or substance abuse; and dementia, according to DSM-IV criteria (American Psychiatric Association 2000). After a complete description of the study, written informed consent was obtained from all participants.

Cognitive/behavioural assessment and MCI classification

The neuropsychological battery included the Mini Mental State Examination (Folstein et al. 1975), as a test of general cognition, and specific tests to assess the following 5 cognitive domains: verbal memory (Story Recall Test and the immediate and delayed recall of Rey's Auditory Verbal Learning Test) (Spinnler and Tognoni 1987; Carlesimo et al. 1996); language (Token Test for verbal comprehension and the naming subtest of the Aachener Aphasie Battery) (Spinnler and Tognoni 1987; Luzzatti et al. 1994); selective and divided attention (Visual Search and Trial Making Test parts A and B) (Spinnler and Tognoni 1987; Giovagnoli et al. 1996); executive functions (Phonemic Fluency Test, Raven's Colored Progressive Matrices and

the Frontal Assessment Battery) (Carlesimo et al. 1996; Appollonio et al. 2005), and visuo-constructional abilities (Copy Drawing Test and the position discrimination subtest of the Visual Object and Space Perception Battery) (Spinnler and Tognoni 1987; Warrington and James 1991). Details regarding administration procedures and Italian normative data for score adjustment, based on age and education as well as normality cutoff scores ($\geq$95 % of the lower tolerance limit of the normal population distribution) were available for each battery test (Spinnler and Tognoni 1987; Luzzatti et al. 1994; Carlesimo et al. 1996; Giovagnoli et al. 1996; Appollonio et al. 2005; Warrington and James 1991). Different MCI subtypes were classified according to modified Petersen's criteria (Winblad et al. 2004), as follows: (1) single, non-memory MCI, subjects with a deficit in a single (other than memory) domain, defined as abnormal test performance (under normality cutoff) in 1 non-memory test; (2) aMCI, subjects with selective memory deficits, defined as a pathological score in at least 1 standardized memory test, with no deficits in other cognitive tests; (3) aMCI multidomain, subjects with 1 abnormal test in at least 2 domains, one of which was memory impairment, and (4) naMCI multidomain, subjects with 1 abnormal test in at least 2 domains, excluding memory. The common criteria for all MCI subtypes were: (a) cognitive deterioration, representing a decline from a previously higher ability level (Clinical Dementia Rating = 0.5) (Hughes et al. 1982); (b) preserved general cognitive functions (Mini Mental State Examination age- and education-adjusted score $\leq$23.8) (Folstein et al. 1975); (c) no impairment or minimal impairment of the basic activities of daily living (ADL) (Katz et al. 1963). Regarding impairment of instrumental ADL (IADL) (Lawton and Brody 1969), this occurs frequently in PD, due to motor rather than cognitive impairment, and this feature was not adopted with the MCI criteria; and (d) no dementia according to the DSM-IV criteria (American Psychiatric Association 2000). Only a global aMCI (including aMCI and aMCI multidomain subtypes) versus naMCI classification (including single, non-memory MCI and naMCI multi-domain subtypes) was operational in the current analysis.

NPS were evaluated in a separate session with respect to cognitive evaluation, using the Neuropsychiatric Inventory (NPI) (Cummings et al. 1994), a fully structured caregiver interview with 12 sub-scales, measuring 12 specific NPS. Each sub-scale is rated on a four-point frequency and on a three-point severity scale, producing a composite score which ranges from 0 and 12 for each symptom. The total composite NPI score ranges between 0 and 144, with higher scores indicating greater behavioural burden. To evaluate the presence/absence of each NPI domain, the composite score was dichotomised (i.e., domain

present = *frequency* × *severity* score ≥ 1). Lastly, functional status was assessed with the ADL (Katz et al. 1963) and IADL scores (Lawton and Brody 1969), while somatic comorbidity was quantified by the Cumulative Illness Rating Scale (CIRS) severity index (Parmelee et al. 1995).

Statistical analysis

Descriptive data were analyzed by one-way analysis of variance (ANOVA) with Scheffe's post hoc test and Chi-square test, as appropriate. The association between the presence of each NPI symptom and either PD-aMCI or PD-naMCI was investigated, using multiple logistic regression models, with PC-cn as the reference category. Covariates included demographics, ADL and IADL scores, CIRS and UPDRS-ME scores. The results were further adjusted for the total daily LED, psychotropic drug use and specific neurological signs. The odds ratios (ORs) with 95 % confidence intervals (CIs) were calculated for these analyses. All tests were two-tailed; the statistical significance was set at $p \leq 0.05$.

Results

ANOVA revealed a significant age- and education-effect between groups (for both variables, $p \leq 0.001$). Scheffe's post hoc analysis revealed that PD-cn were significantly younger and higher educated than PD-aMCI and PD-naMCI. Overall, ADL, IADL, MMSE, and CIRS scores significantly differed among groups (for all comparisons, $p \leq 0.001$). Post hoc analysis revealed that PD-aMCI and PD-naMCI had significantly higher ADL and IADL scores and lower MMSE scores compared to PD-cn, while only PD-aMCI had a higher CIRS score than PD-cn (Table 1).

Regarding motor impairment between groups, Scheffe's post hoc pairwise comparison revealed that PD-aMCI and PD-naMCI had significantly higher UPDRS-ME scores than PD-cn; postural instability appeared to be the only motor sign which significantly differed between groups, being more frequent in PD-aMCI than in PD-cn (Table 2). After Scheffe's post hoc analysis, the total daily LED significantly differed in PD-aMCI and PD-naMCI compared to PD-cn. Concerning psychotropic drug use, antipsychotics were significantly more used by PD-aMCI and PD-naMCI than PD-cn, while antidepressants were significantly more used by PD-aMCI than PD-cn. Lastly, anxiolytic drug use did not differ between the groups (Table 2).

After Scheffe's post hoc pairwise comparisons, patients with PD-aMCI had a significantly higher composite score than PD-cn in most NPI items, including: delusions, hallucinations, irritability, depression, apathy, aberrant motor behaviour, appetite disturbances and the total NPI score, while PD-naMCI subjects were not significantly different from PD-cn subjects (Table 3). Depression, sleep disturbance, anxiety and apathy were (in this order) more frequent NPS in PD-MCI. Subjects with PD-aMCI displayed a significant higher frequency of delusions, hallucinations, irritability, depression, aberrant motor behaviour and appetite disturbance than PD-cn. Hallucinations and irritability were significantly more frequent in PD-naMCI than in PD-cn (Table 3).

Multiple logistic regression analysis, with PD-cn as a reference group, revealed that PD-aMCI and PD-naMCI were significantly associated with the presence of hallucinations (OR of 3.9 [95 % CI 1.2–13.3], and OR of 3.6 [95 % CI 1.0–12.9] respectively) and irritability (OR of 3.0 [95 % CI 1.5–6.2] and OR of 2.4 [95 % CI 1.1–5.0] respectively). However, controlling for the total daily LED revealed that only irritability remained significantly associated with PD-aMCI (OR of 3.0 [95 % CI 1.6–56]) and PD-naMCI (OR of 2.2 [95 % CI 1.1–4.4]). The further inclusion of covariates of antipsychotic drug use and the

Table 1 Demographics and functional characteristics, global cognition (MMSE), and comorbidity (CIRS) scores of cognitively normal PD, PD-aMCI and PD-naMCI

	PD-cn ($n = 164$)	PD-aMCI ($n = 142$)	PD-naMCI ($n = 104$)
Male, n (%)	100 (61.0)	81 (57.0)	66 (64.0)
Age, years	64.9 (9.8)	69.9 (8.7)[***]	71.0 (8.5)[***]
Education, years	8.4 (4.6)	7.2 (4.7)[*]	5.9 (3.4)[***]
ADL lost, n	0.2 (0.5)	0.7 (0.8)[***]	0.6 (0.8)[**]
IADL lost, n	0.4 (0.7)	1.1 (1.1)[***]	0.9 (1.0)[***]
MMSE score	28.5 (1.5)	26.3 (1.9)[***]	27.0 (2.0)[***]
CIRS score	19.6 (2.7)	20.9 (2.9)[***]	20.1 (3.0)

Except for gender distribution, figures are means (SD)

MMSE mini mental state examination, *CIRS* cumulative illness rating scale, severity score, *PD* Parkinson's disease, *aMCI* amnestic mild cognitive impairment, *naMCI* non-amnestic MCI, *ADL* activities of daily living, *IADL* instrumental ADL

Significant differences at pair comparison (one-way analysis of variance with Scheffe's post hoc test) are asterisked (compared to PC-cn group) as follows: [*]$p \leq 0.05$; [**]$p \leq 0.01$; [***]$p \leq 0.001$

Table 2 UPDRS-ME score and prevalence of Parkinsonian signs, LED and prevalence of psychotropic drugs use of cognitively normal PD, PD-aMCI and PD-naMCI

	PD-cn ($n = 164$)	PD-aMCI ($n = 142$)	PD-naMCI ($n = 104$)
UPDRS-ME score	18.6 (10.1)	25.1 (12.6)[***]	24.4 (12.2)[***]
Rigidity	156 (95.1)	137 (96.5)	99 (95.2)
Rest tremor	107 (65.2)	96 (67.6)	74 (71.2)
Postural instability	43 (26.2)	74 (52.1)[***]	32 (30.8)
LED, mg/day	289.5 (170.2)	367.8 (219.7)[**]	359.6 (197.9)[*]
Antipsychotic drugs use	5 (3.0)	22 (15.5)[***]	11 (10.6)[*]
Antidepressant drugs use	29 (17.7)	46 (32.4)[**]	18 (17.3)
Anxiolytics drugs use	47 (28.7)	42 (29.6)	25 (24.0)

Except for UPDRS-ME score and LED were figures are means (SD), results are presented as n (%)

UPDRS-ME unified Parkinson's disease rating scale-motor examination, *LED* total daily levodopa equivalent dose, *PD* Parkinson's disease, *aMCI* amnestic mild cognitive impairment, *naMCI* non-amnestic MCI

Significant differences at pair comparison (one-way analysis of variance with Scheffe's post hoc test or Chi square test) are asterisked (compared to PC-cn group) as follows: [*] $p \leq 0.05$; [**] $p \leq 0.01$; [***] $p \leq 0.001$

Table 3 Mean composite scores (*frequency × severity*) and presence of each Neuropsychiatric Inventory (NPI) symptom in cognitively normal PD, PD-aMCI and PD-naMCI

NPI item	PD-cn ($n = 164$)		PD-aMCI ($n = 142$)		PD-naMCI ($n = 104$)	
	Mean (SD)	Item present, n (%)	Mean (SD)	Item present, n (%)	Mean (SD)	Item present, n (%)
Delusions	0.04 (0.4)	2 (1.2)	0.3 (1.5)[*]	10 (7.0)[**]	0.06 (0.5)	3 (2.9)
Hallucinations	0.1 (0.7)	5 (3.0)	0.7 (1.8)[**]	23 (16.2)[***]	0.3 (1.3)	10 (9.6)[*]
Agitation/aggression	0.3 (1.2)	15 (9.1)	0.7 (2.1)	23 (16.2)	0.4 (1.2)	13 (12.5)
Disinhibition	0.02 (0.3)	1 (0.6)	0.2 (1.4)	3 (2.1)	0.05 (0.6)	1 (1.0)
Irritability	0.6 (1.5)	24 (14.6)	2.0 (3.1)[***]	54 (38.0)[***]	1.2 (2.3)	33 (31.7)[**]
Depression	2.8 (3.2)	90 (54.9)	3.7 (3.3)[*]	100 (70.4)[**]	2.9 (3.1)	63 (60.6)
Anxiety	2.9 (3.3)	90 (54.9)	3.4 (3.5)	86 (60.6)	2.7 (3.1)	58 (55.8)
Apathy	2.1 (2.5)	74 (45.1)	3.1 (3.4)[**]	77 (54.2)	2.4 (2.9)	49 (47.1)
Euphoria	0.05 (0.4)	3 (1.8)	0.1 (0.8)	5 (3.8)	0	0
Aberrant motor behaviour	0.1 (0.8)	4 (2.4)	0.5 (1.7)[*]	12 (8.5)[*]	0.2 (0.8)	3 (2.9)
Sleep disturbance	3.8 (3.8)	94 (57.3)	3.9 (3.4)	95 (66.9)	3.4 (3.6)	62 (59.6)
Appetite disturbance	0.5 (1.6)	16 (9.8)	1.2 (2.9)[*]	27 (19.0)[*]	0.8 (1.7)	18 (17.3)
Total score	13.3 (11.0)	–	19.8 (15.8)[***]	–	14.1 (11.2)	–

PD Parkinson's disease, *aMCI* amnestic mild cognitive impairment, *naMCI* non-amnestic MCI

Significant differences at pair comparison (one-way analysis of variance with Scheffe's post hoc test or Chi square test) are asterisked (compared to PC-cn group) as follows: [*] $p \leq 0.05$; [**] $p \leq 0.01$; [***] $p \leq 0.001$

presence of postural instability (the latter included instead of the UPDRS-ME score) did not modify the results.

Discussion

As far as we know, this is the first study examining the NPS profile in PD subjects with aMCI and naMCI. According to the findings of this study, PD-aMCI is generally characterised by a greater NPS burden than PD-naMCI, even if both PD-MCI groups showed higher mean composite NPI scores and a higher frequency of NPS compared to PD-cn.

The most common NPS experienced by PD-MCI subjects were: depression (65.5 %), sleep disturbance (63.3 %), anxiety (58.2 %) and apathy (50.7 %). Specifically, irritability was significantly related to PD-aMCI and PD-naMCI, as compared to PD-cn. Our data cannot determine whether the presence of this NPS in PD-MCI reflects changes in the brain or whether it indicates a subjective reaction to the cognitive changes. The negative association between hallucinations and PD-MCI, after controlling for LED, might be explained by the fact that these subjects took a higher levodopa daily dose than PD-cn, with a subsequent higher risk of developing hallucinations.

The authors of a recent study including 48 subjects with PD-MCI (Leroi et al. 2012) found no overall relevant differences between this group and PD-cn, even if apathy was more frequent in PD-MCI than with PD-cn as being of significance in differentiating the two groups. Unfortunately, the relatively small sample size in Leroi's study did not permit these authors to evaluate the different NPS profile of PD-aMCI and PD-naMCI subjects. Differences between Leroi's study and our study are probably due to the heterogeneity of the cognitive assessment for diagnosing MCI, to differences in study setting and to differences in the duration and stage of PD included.

Some strengths of this study include: its large sample size, the use of a standardized diagnostic procedure and adjustment for multiple potential confounding factors, including total daily LED, psychotropic drug use and neurological symptoms. However, residual and unmeasured confounding factors cannot be excluded. Furthermore, the cross-sectional design of the study may not be optimal since behavioural disturbances can fluctuate and may not be present at every examination. Finally, due to the cross-sectional study design, a relationship between the type of cognitive impairment in PD and NPS expression can only be hypothesized. Longitudinal data on large samples of subjects, coupling clinical, cognitive-behavioural and imaging data, are required to evaluate the prognostic role of NPS in PD subjects with MCI.

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