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Article type : Original Article

Parkinson disease with mild cognitive impairment: domain-specific cognitive complaints predict dementia

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Keywords: cognitive complaint, mild cognitive impairment, dementia, Parkinson´s disease

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Number of tables: 5
Word count abstract: 248
Word count paper: 2993

Running head: Predictive value of cognitive complaints in PD

ABSTRACT

Background: The presence of subjective cognitive complaints (SCC) as a predictor of cognitive impairment in Parkinson´s disease (PD) has shown conflicting results. Most previous studies only assessed complaints in the memory domain. We investigate the association of SCCs across cognitive domains with development of mild cognitive impairment (PD-MCI) and dementia (PDD) in PD, and to assess agreement between SCCs and objective cognitive impairments in this population.

Methods: This is a retrospective analysis of a prospective cohort study. Participants were enrolled at six North-American movement disorders centers. They underwent neuropsychological and non-cognitive clinical evaluations, including the modified Neurobehavioral Inventory to elicit SCC (rated by each patient and independently by their close contact (CC)). Associations between SCCs and development of future cognitive impairment were assessed. Agreement between SCCs and objective impairment within the same domain was also calculated.

Results: Of 138 included PD patients, 42% fulfilled criteria for PD-MCI. None of the NBI items predicted development of cognitive impairment after one and two years in PD with normal cognition. In PD-MCI patients, SCCs related to attention predicted dementia at year one. CC ratings of SCCs related to memory and language problems predicted PDD in PD-MCI patients. According to CC reported patients' complaints, there was a significant agreement between SCCs and objective cognitive test scores on attention.

Conclusions: Eliciting SCCs including cognitive domains other than memory is crucial for a complete evaluation, including both patient and CC report. Memory,

language and especially attention SCCs in PD-MCI may predict progression to dementia.

INTRODUCTION

Mild cognitive impairment (MCI) and dementia are well-recognized entities in Parkinson's disease (PD). MCI is characterized by cognitive deficits with no effect on daily functioning, but a subjective cognitive complaint (SCC) is needed for the diagnosis.[1] This entity represents an intermediate state between normal cognition and dementia. Its frequency ranges from 20% to 65% among PD patients [2,3]

In the general aging population as well as in PD,[4] SCCs are very common. Increasing evidence links subjective decline with an increased risk for future cognitive decline and Alzheimer's disease (AD).[5-7] Therefore, in non-cognitively impaired subjects, SCCs may reflect subtle cognitive deficits. However, the presence of cognitive complaints as a predictor of cognitive impairment in PD has shown conflicting results. Erro[8], Hong[9] and Galtier[10] found that the presence of cognitive complaints predicted PD-MCI after 2, 2.5 and 7.5 years of follow up, respectively. Conversely, we recently found no association between SCC and cognitive impairment at the time of the evaluation or cognitive decline after one and two years of follow up in individuals with PD without dementia (PD with normal cognition [PD-CN] and PD-MCI).[11] These conflicting findings might correspond to the methodology used. The first three studies based the presence of cognitive complaints only on the existence of memory complaints and used PD-MCI criteria level I, which provide less diagnostic certainty than level II criteria. In our previous study, we used several methods of eliciting cognitive complaints, covering cognitive complaints in attention, memory, executive function, language and non-verbal skills, and applied PD-MCI level II criteria.[11] According to previous studies, memory complaints may be particularly predictive of future cognitive decline in PD. Since cognitive impairment in PD is heterogeneous and may involve different cognitive domains, it is important to understand the role of complaints in

other domains as a potential marker of cognitive decline. In addition, specific cognitive complaints that predict Parkinson's disease dementia (PDD) in PD-MCI have not been evaluated and might represent a marker of progression to dementia in this population.

Gradual cognitive decline is required as a part of the diagnosis of PD-MCI and can be inferred from SCCs reported by either the patient or the informant or may be observed by the physician. Copeland et al. showed a moderate level of agreement in PD-MCI patients' and care partners' subjective reports for memory, language, visuospatial skills, and executive functioning, but not for attention.[12] However, we recently found in a sample of persons with PD without dementia (both PD-CN and PD-MCI) that there was statistically significant agreement between the CC report of subjective complaints and the patient-reported measures but kappa values were low (<0.2).[11] Therefore, for cognitive assessment in PD, a CC interview about patient cognitive changes might be an important adjunct to the patient's report. In the current study we investigated the association between specific cognitive complaints and the concurrent presence of PD-MCI. Second, we investigated the association between specific cognitive complaints and the development of PD-MCI and PDD after one and two years of follow up. Third, we measured the agreement (according to presence or absence) among specific cognitive complaints and cognitive domain impairments on neuropsychological testing.

METHODS

Subjects

A non-consecutive, convenience sample of English-speaking persons with PD without dementia were enrolled at six North American tertiary care movement disorders centers for a prospective study of PD-MCI screening measures. This is a retrospective analysis of the longitudinal cohort study. The recruitment period was from December 2008 to June 2011. Other inclusion and exclusion criteria have been reported previously.[13] Written informed consent was obtained from all study participants and participating informed contacts (defined as contact at least twice weekly) before formal screening and study visits. PD patients received an annual

clinical evaluation followed 1–3 weeks later by formal neuropsychological testing performed blinded to clinical results.

The Ethics Committee of each institution approved the study.

Data collection

Evaluation of non-cognitive PD signs and symptoms and neuropsychological testing was performed at a similar time of day and participants were evaluated in the ON state. PD patients with significant depression (a score of 5 or greater) according to the 15-item geriatric depression scale (GDS-15) were excluded (n=4). SCCs were elicited using a modified Neurobehavioral Inventory (NBI) (Professional Resources and Technologies, Westtown, PA, supplementary methods), a list of 19 cognitively based problems with everyday life. Complaints are grouped in domains related to attention (trouble sustaining attention, trouble listening well, easily distracted), executive function (trouble finishing tasks, trouble sequencing steps, poorly organized/unable to plan), memory (forgetting recent events, forgetting remote events, forgetting names, forgetting appointments, forgetting medications, forgetting where objects are placed), language (trouble naming, rambling, trouble understanding conversations, trouble understanding what is read) and non-verbal skills (getting lost, finding multiple step activities confusing, dressing confusion). This was administered to patients and close contacts (CC) separately. Questions aimed to identify if a problem was present. The problem was considered as present only in the case of being new and not present the subject's whole life.[11,13,14]

Each new problem is given a score of one point. Patients free of cognitive complaints would have a score of 0, and the higher score the more cognitive complaints. We also used other methods for eliciting SCC,[11] but we use the NBI for the current analysis as it assesses SCC across specific cognitive domains.

Impairment of functional independence related to cognitive problems was assessed by the Disability Assessment for Dementia[15] administered to the CC.

When one or more items of the questionnaire were impaired due to cognition, the patient was classified as having dementia. This was modified to specify whether or not impairment related to cognitive problems or to physical limitations and only impairment secondary to cognitive problems was accepted as evidence of functional impairment. The Movement Disorders Society United Parkinson's Disease Rating Scale (MDS-UPDRS) was administered by a movement disorders neurologist.

Diagnosis of Cognitive impairment

Diagnosis of PD-MCI was defined as a score of 1.5 SD or more below the normative mean on at least two neuropsychological tests to align with the MDS Task Force Level II criteria.[16] Since we aimed to evaluate the prognostic value of SCCs, the MCI diagnosis was made solely on the basis of the neuropsychological findings, regardless of the presence of subjective cognitive complaints. PDD was diagnosed according to MDS criteria. This was defined as an impairment in at least two cognitive domains that represents a decline from premorbid level and is severe enough to impair functional independence.[17]

Neuropsychological Assessment

The neuropsychological assessment included two tests from 5 different cognitive domains. 1) Attention: the Delis Kaplan Executive Function System (DKEFS) Color Word Interference Color Naming test[18] and the Wechsler Memory Scale-III letter-number sequencing test[19], 2) Language: the DKEFS Verbal Fluency Category Fluency test[18, 20] and the 30-item Boston Naming Test[21]; 3) Executive function: the Trail Making Test B minus A[22] and the Visual Verbal Test abbreviated 10-item version[23], 4) Memory: the Rey Complex Figure Test and Recognition Trial (RCFT) Delayed Recall[24] and the California Verbal Learning Test-II Long Delay Free Recall test; [25] 5) visuospatial function: the Benton Judgment of Line Orientation test[26] and the Copy Trial of the RCFT[26]

Data Analysis

Our analysis was divided in three parts.

First, in order to assess the association between each cognitive complaint and PD-MCI diagnosis at baseline, we used a X^2 test and quantified the association using odds ratios (OR).

Second, using the same statistical test, we studied the association between specific cognitive complaints at baseline and development of either PD-MCI or PDD in patients who were PD-CN at baseline, and PDD in PD-MCI after 1 and 2 years of follow up. A logistic regression analysis was performed for significant associations between specific cognitive complaints and prediction of PD-MCI or PDD (after adjustment for multiple comparisons). Potential confounders for cognitive impairment (age, education and sex) were included.

Third, we measured the agreement among objective impairment in specific cognitive domains and specific cognitive complaints (according to presence or absence) using a kappa coefficient (*k*). An impairment of a cognitive domain was considered present when Z-score of at least one of the two test values was at least 1.5 SD or more below the normative mean.

Within each of the 3 parts of this study, we defined the threshold for statistical significance as 0.05 divided by the number of statistical tests performed. This was 0.0026 for the first and second analysis, whereas in the third analysis the threshold was different among the cognitive domains due to the different number of SCC questions related to each domain (memory= 0.01, attention= 0.017, executive function= 0.017, language= 0.0125, non-verbal= 0.017).

Statistical analyses were performed with SPSS 20 software (IBM, Armonk, NY).

RESULTS

Demographics

Data on 138 patients were included at baseline. At year 1, 121 patients were assessed for follow up and, at year 2, 109. The median age at baseline was 71 (range 60-84) and median time from diagnosis was four (range 1-29) years. Fifty-seven (41%) patients met criteria for diagnosis of PD-MCI at baseline since they had impairment on two or more tests of the core neuropsychological test battery. Demographic, motor and other clinical features of the patients at baseline and follow up are listed in Table 1.

After one year of follow up 18 (25.71%) PD-CN patients converted to PD-MCI or

dementia and 9 (17.65%) PD-MCI patients converted to PDD. At year 2, 13 (23.61%) PD-CN baseline patients converted to PD-MCI or PDD and 10 (22.22%) PD-MCI patients converted to PDD (Figure 1).

The CC included spouses in the majority of cases (71%) being less common, children (15%), friend/neighbor (9%) and sibling, partner/girlfriend (2% each). In addition, isolated cases of daughter-in-law and roommate were included as informants.

1. Association between Cognitive Complaint and PD-MCI diagnosis at baseline.

There were no specific cognitive complaints significantly associated with PD-MCI after adjustment for multiple comparisons. Before adjustment for multiple comparisons several questions were associated with cognitive impairment (Supplementary table 1)

2. *Association between Cognitive Complaint in PD-CN at baseline and progression to MCI or dementia at year 1 and 2.*

None of the NBI items predicted development of cognitive impairment after 1 and 2 years in individuals who were PD-CN at baseline. Supplementary tables 2 and 3 show which of the questions predicted cognitive impairment in this group of patients before multiple comparisons adjustment.

3. *Association between Cognitive Complaint in PD-MCI at baseline and progression to PDD at year 1 and 2.*

In individuals determined to have PD-MCI at baseline, patient-reported inattentiveness at year 1 was associated with development of PDD at year 1 (p=0.001, OR=16; table 2), after adjusting for potential confounders there was a trend towards significance (p=0.051, OR=2.46). No patient-reported SCC at baseline were associated with development of PDD at year 2 (Table 3). Close contact-reported SCC about forgetting medications, difficulty understanding conversations, and difficultly understanding what is read was associated with PDD at year 1 (p=0.001, OR=16; p=0.002, OR=20.5, and p= 0.002, OR=1.29, respectively; table 2). The two first SCC remained significant after adjusting for confounders: forgetting medications (OR=23,26; p=0.003) and difficulty understanding

conversations (OR=38,46; p=0.01). At year 2 CC reported SCC for forgetting medications was also associated with PDD (p=0.001, OR=2.68, table 3), this was also significant after adjusting for confounders (OR=66,67, p=0.003)

4. *Agreement between subjective complaints and objective cognitive impairments within the same domain*

In PD-MCI patients, there was no statistically significant agreement between subjective complaints and objective cognitive impairments within the same domain. See table 4 for significant agreement before adjusting for multiple comparisons. According to CC reported patients' complaints, agreement for the presence of a cognitive complaint occurred more frequently than by chance between attention questions related to trouble listening well and easily distracted and attention domain impairment (both comparisons p=0.002, kappa=0.387, fair agreement)[27]. Before multiple comparisons correction, there was also significant agreement between domains-specific cognitive complaints and objective cognitive test scores (see table 5).

DISCUSSION

Considering the contradictory results of previous reports about the relationship between cognitive complaints and development of objective cognitive impairment in PD and the limited examination of complaints outside the memory domain, we aimed to find if SCCs beyond memory complaints could predict cognitive decline in PD. For this purpose, we used the NBI questionnaire that allows for the description of specific domains of complaint and is very clear for tabulating the type and number of items. This inventory has been used reliably in multicenter patient samples and related analyses [11,13,14]

Our main finding was that specific SCCs are associated with dementia in patients with PD-MCI. Regarding patients' complaints, PD-MCI subjects who considered themselves inattentive had a higher risk of developing PDD after one year (p=0.051). However, according to CC related to patients, language difficulties (understanding conversations) and memory complaints about forgetting to take their medications predicted decline after one year of follow up. Interestingly,

attention deficits are very prominent in PDD, therefore, it is plausible that attention complaints could be an early sign of this typical deficit prior to progression to dementia.[28] Language comprehension complaints were only reported by the CC. Even though processing and comprehension of complex grammar and syntax appear in PD, they are not usually evaluated in the neuropsychological assessment.[29] Also, there is usually lack of awareness of language difficulties.[30,31] The third complaint that predicted progression to dementia was forgetting to take one's medications, also reported by the CC and not by the patient. This specific memory compliant heralds loss of personal autonomy that defines the diagnosis of dementia. The Pill Questionnaire,[32] has been proposed as a way to probe this function, and is rated by direct observation of medication reporting by the interviewer and if necessary corroborated by a caregiver. Even though this questionnaire is neither sensitive nor specific as the sole screening tool for PD-MCI or as a measure of functional impairments,[32] inaccurate medication reporting by the CC in the presence of a diagnosis of PD-MCI has been shown to predict development of dementia in the next year.[33,34] This is in keeping with our results.

In the second part of the study we investigated the agreement between subjective and objective cognitive impairment in PD-MCI. Interestingly, we found a fair agreement between attention SCCs (trouble listening well and easily distracted) according to CC complaints and attention domain impairment, but not with patients´ complaints. As PD-MCI patients may be unaware of their cognitive deficits[30,31] and there is no agreement in attention complaints between patients and CC reports[12,13], we emphasize that it is important to elicit SCCs from patients and CC. Unexpectedly, we found slight agreement between patients´ complaints about forgetting names and visuospatial impairment and no statistically significant agreement for the rest of the variables. Even though these measures seem to be independent, difficulty naming along with visuospatial deficits are reported to be characteristic of the typical cortical dysfunction that appears in the transition to dementia in PD.[35]

Finally, regarding PD-CN subjects, we did not find any SCCs that predicted cognitive deterioration. Results may have been affected by sample size or the *a*

priori decision to apply Bonferroni corrections, which some authors feel is too stringent.[36] If considering study results prior to application of the Bonferroni correction, patient-reported concerns regarding understanding and difficulty remembering medications could both predict cognitive deterioration in PD-CN individuals. It is plausible that these concerns may have particular value given that they had statistically significant associations with development of PDD when reported in individuals with PD-MCI.

The main limitation of the present study is the number of PD patients assessed. The number of patients who converted to PD-MCI or dementia at 1 and 2 years was similar to what has been previously reported,[37] however considering that PD-MCI is a very heterogeneous entity, it is likely that we need a larger sample of PD-CN to predict different PD-MCI subtypes, and the relationships between SCCs and objective deficits may differ across subtypes. Unlike those individuals with amnestic MCI leading to dementia associated with AD neuropathology, PD-MCI shows more widespread, multidomain impairments while memory impairment does not always occur.[3,38] This heterogeneity may underlie different pathophysiological substrates. Even though the subtypes of cognitive impairment in PD are not well defined yet, the longitudinal CamPaIGN study in provides a strong argument for this. persons with PD without dementia were classified as a frontostriatal/executive or posterior cortical (language and visuospatial deficits) dysfunction profile, the latter predicted dementia within 5 years of PD diagnosis.[39] Of note, cognitive functions and subjective memory complaints in PD patients can be affected by presence of depression. However, our study excluded patients with significant depression at baseline.[40, 41]

The main strength of our work is that we assessed presence of SCCs not only in the memory realm but also within the other main cognitive domains (i.e. attention, executive function, language and non-verbal cognitive functions). The importance of the evaluation of specific cognitive complaints is that they are not only related to memory and reflect new subjective difficulties that may herald dementia in PD. This is an easy assessment that could be considered to be included in the formal neuropsychological assessment. Also, as opposed to some other studies that applied level I MDS criteria for PD-MCI diagnosis[8-10] we applied level II criteria that

seem to be more accurate since they include a comprehensive neuropsychological assessment evaluating the five cognitive domains.[16]

We can conclude that eliciting SCCs from both patients and contacts that assess different domains is crucial for a complete evaluation of cognition in PD. Our findings suggest that whereas patients´ complaints related to inattention may predict progression to dementia in PD-MCI, they might not be aware of deficits in memory and language reported by their CC. In this regard, forgetting medications and difficulties understanding seem to be associated with the emergence of dementia in the short term. Therefore, we conclude that eliciting cognitive complaints including all cognitive domains and not only memory, may help to predict cognitive outcome. This is an easy and short evaluation that should be administered to both patient and CC. These results require replication with a larger sample allowing investigation of these relationships within subtypes of PD-MCI.

Acknowledgements

We acknowledge the patients for their collaboration in the study.

Conflict of Interest and Sources of Funding Statement

The authors report no conflict of interest regarding the study

Funding Statement

Michael J Foundation for Parkinson's Research

The Canadian Institutes of Health Research

Data Availability Statement

Data of this work is available upon reasonable request to the corresponding author

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Figure legend:

Figure 1: Graphical summary of of conversion and reversion rates at year and and 2 of follow up according to PD cognitive diagnosis at baseline.

BL= baseline, PD- CN= Parkinson´s disease with normal cognition, PD-MCI= Parkinson´s disease with mild cognitive impairment, PDD= Parkinson´s disease with dementia. Y1= year 1, Y2= year 2

Table 1. Baseline Characteristics

	Baseline	1 year	2 years
Total no.	138	121	109
Age, y (median, range)	71.06 (5.44)	71.02 (5.37)	70.82 (5.22)
Gender, % male	67	68	67
Education, y (median, range)	15.82 (2.52)	15.92 (2.42)	16.01 (2.43)
Estimated premorbid IQ	113.20 (9.01)	113.48 (9.03)	114.41 (8.38)
Time since diagnosis, y (median, range)	4 (4.59)	4.77 (4.02)	4.76 (4.04)
Total MDS-UPDRS (median, range)	43 (16.83)	45(16.59)	44(15.90)
MDS-UPDRS-III (median, range)	26.80 (11.28)	30(11.47)	26.50(11.10)
Total LEU, mg (median, range)	414 (358.38)	500 (336.35)	600(342.19)
MoCA total score (median, range)	25.2 (2.93)	26(2.90)	26(2.77)
SCOPA-Cog (median, range)	27.50(4.84)	28(4.74)	29(4.81)
MMSE (median, range)	28.30 (1.83)	29(1.81)	29(1.67)
PD-MCI			
Relative to estimated premorbid IQ* (N,%)	110 (79.7)	94 (78)	69(66)
Relative to population norms ** (N,%)	57 (41.30)	40 (28.8)	31 (22.33)
Parkinson disease dementia * (N%)**	-	11 (9.09)	8 (7.3)
Geriatric Depression scale (median, range)	1.30 (1.31)	1 (1.26)	2(1.30)
Cognitive complaint measures			
NBI-Subject # with no complaint	55 (39.80)	38 (31.93)	28 (26.92)
NBI-Subject # with one complaint	25 (18.10)	27 (22.68)	24 (23.07)
NBI-Subject # ≥2 complaint	58 (42)	56 (47.05)	52 (50)
NBI-Close Contact # with no complaint	97	76	72
NBI-Close Contact # with one complaint	24	20	7
NBI-Close Contact # ≥2 complaint	17	24	25
General complaint question (N answering yes, %)	54 (39)	51(46)	51(49)
UPDRS 1.1 (N with score>0,%)	45(32)	51(42)	40(38)

MCI, mild cognitive impairment; MDS-UPDRS-III, Movement Disorders Society United Parkinson's Disease Rating Scale, part 3; LEU, levodopa equivalent units; MoCA, Montreal Cognitive Assessment; SCOPA-Cog, Scale for Outcomes in Parkinson's Disease-Cognition; MMSE, Mini-Mental State Examination.

*Impairment on neuropsycholoical tests defined as 1.5 SD below expected performance based on Wechsler Test of Adult Reading

**Impairment on neuropsychological tests defined as 1.5 SD below population norms

***Diagnosis of Parkinson's disease dementia is when a person is originally diagnosed with Parkinson's based on Queen Square Brain Bank criteria and followed by dementia symptoms that appear a year or more later

Table 2. Association between Cognitive Complaint in PD with Mild cognitive Impairment (PD-MCI) at baseline and conversion to dementia at year 1

NBI item	Patient			Close contact		
	PD-MCI stable (n=42) [N (%)]	*PD-MCI converters (n=9) [N (%)]*	*p-value and OR (2x2)*	*PD-MCI stable (n=42) [N (%)]*	*PD-MCI (n=9) converters [N (%)]*	*p-value and OR (2x2)*
Memory						
1.Forgetting recent events	8 (19%)	2 (22%)	0.828 (1.21)	*4 (9.5%)*	*4 (44%)*	*0.009 (7.6)*
2.Forgetting remote events	6 (14.3%)	2 (22%)	0.552 (1.71)	5 (11.9%)	3 (33%)	0.109 (3.7)
3.Forgetting names	8 (19%)	4 (44%)	0.103 (3.40)	7 (16.7%)	2 (22%)	0.692 (1.43)
4.Forgetting appointments	0 (0%)	0 (0%)	NA	2 (4.8%)	3 (33%)	*0.009 (10.00)*
5. Forgetting medications	2 (4.8%)	2 (22%)	0.077 (5.71)	2(4.8%)	4 (44%)	**0.001(16.00)**
6. Forgetting where objects are placed	5 (11.9%)	2 (22%)	0.414 (2.11)	*8 (19%)*	*6 (67%)*	*0.004 (8.5)*
Attention						
1. Trouble sustaining attention	4 (9.5%)	0 (0%)	0.335 (0.91)	4 (9.5%)	4 (44%)	*0.009 (7.6)*
2. Trouble listening	2 (4.8%)	4 (44%)	**0.001 (16.00)**	5 (11.9%)	1 (11%)	0.947 (0.93)
3. Well easily distracted	3 (7.1%)	0 (0%)	0.409 (0.93)	5 (11.9%)	1 (11%)	0.947 (0.93)
Executive						
1.Trouble finishing tasks	5 (11.9%)	2 (22%)	0.414 (2.11)	3 (7.1%)	2 (22%)	0.167 (3.71)
2. Trouble sequencing steps	1 (2.4%)	1 (11%)	0.221 (5.13)	0 (0%)	0 (0%)	NA
3. Poorly organized/unable to plan	2 (4.8%)	0 (0%)	0.504 (0.95)	*3 (7.1%)*	*3 (33%)*	*0.027 (6.50)*
Language						
1.Trouble naming	7 (16.7%)	3 (33%)	0.253 (2.50)	4 (9.5%)	4 (44%)	*0.009 (7.60)*
2. Rambling	3 (7.1%)	1 (11%)	0.688 (1.63)	4 (9.5%)	1 (11%)	0.884 (1.19)
3. Trouble understanding conversations	1 (2.4%)	0 (0%)	0.64 (0.98)	1(2.4%)	3 (33%)	**0.002 (20.50)**

4. Trouble understanding what is read	3 (7.1%)	2 (22%)	0.167 (3.71)	0 (0%)	2 (22%)	**0.002 (1.290)**
Non-verbal						
1.Getting lost	0 (0%)	0 (0%)	NA	0 (0%)	0 (0%)	NA
2. Finding multiple step activities confusing	3(33.3%)	0(0%)	0.409 (0.93)	2 (4.8%)	2 (22%)	0.077 (5.71)
3. Dressing confusion	0(0%)	0(0%)	NA	0(0%)	1 (11%)	*0.029 (1.13)*

* The threshold for statistical significant considering correction for multiple comparisons = 0.0026. Statistically significant results are shown in bold type. Statistically significant results before multiple comparisons correction are shown in italics.
- NA= non admitted

Table 3. Association between Cognitive Complaint in PD with Mild cognitive Impairment (PD-MCI) at baseline and conversion to dementia at year 2

NBI item	Patient			Close contact		
	PD-MCI stable (n=35) [N (%)]	*PD-MCI converters (n=10) [N (%)]*	*p-value and OR (2x2)*	*PD-MCI stable (n=35) [N (%)]*	*PD-MCI (n=10) converters [N (%)]*	*p-value and OR (2x2)*
Memory						
1.Forgetting recent events	8 (22.3%)	2 (20%)	0.848 (0.84)	3 (8.6%)	4 (40%)	0.016 (7.1)
2.Forgetting remote events	5 (14.3%)	2 (20%)	0.660 (1.50)	4 (11.4%)	3 (30%)	0.153 (3.32)
3.Forgetting names	9 (25.7%)	3 (30%)	0.787 (1.24)	6 (17.1%)	2 (20%)	0.835 (1.21)
4.Forgetting appointments	0 (0%)	0 (0%)	NA	1 (2.9%)	3 (30%)	*0.008 (14.57)*
5. Forgetting medications	1 (2.9%)	3 (30%)	*0.008 (14.57)*	1 (2.9%)	4 (40%)	**0.001 (22.68)**
6. Forgetting where objects are placed	5 (14.3%)	2 (20%)	0.660 (1.50)	8 (22.3%)	6 (60%)	*0.025 (5.06)*
Attention						
1. Trouble sustaining attention	4 (11.4%)	0 (0%)	0.263 (0.89)	4 (11.4%)	4 (40%)	*0.037 (5.17)*
2. Trouble listening						
3. Well	2 (5.7%)	3 (30%)	*0.031 (7.07)*	4 (11.4%)	1 (10%)	0.899 (0.86)
easily distracted	1 (2.9%)	1 (10%)	0.334 (3.78)	3 (8.6%)	2 (20%)	0.899 (0.86)
Executive						
1.Trouble finishing tasks	3 (8.6%)	3 (30%)	0.079 (4.57)	3 (8.6%)	2 (20%)	0.310 (2.67)
2. Trouble sequencing steps	1 (2.9%)	1 (10%)	0.334 (3.78)	0 (0%)	0 (0%)	NA
3. Poorly organized/unable to plan	2 (5.7%)	0 (0%)	0.439 (0.94)	2 (5.7%)	3 (30%)	*0.031 (7.07)*
Language						
1.Trouble naming	7 (20%)	2 (20%)	1 (1)	4 (11.4%)	4 (40%)	*0.037 (5.2)*
2. Rambling	2 (5.7%)	2 (20%)	0.162 (4.13)	2 (5.7%)	1 (10%)	0.632 (1.83)
3. Trouble understanding conversations	0 (0%)	0(0%)	NA	1(2.9%)	3 (30%)	*0.008 (14.57)*

4. Trouble understanding what is read	3 (8.6%)	2 (20%)	0.310 (0.27)	0 (0%)	2 (20%)	*0.007 (1.25)*
Non-verbal						
1.Getting lost	0 (0%)	0 (0%)	NA	0 (0%)	0 (0%)	NA
2. Finding multiple step activities confusing	2 (5.7%)	0 (0%)	0.439 (0.94)	1 (2.9%)	2 (20%)	0.055 (8.5)
3. Dressing confusion	0(0%)	0(0%)	NA	0(0%)	1 (10%)	0.058 (1.11)

* The threshold for statistical significant considering correction for multiple comparisons = 0.0026. Statistically significant results are shown in bold type. Statistically significant results before multiple comparisons correction are shown in italics.
- NA= non admitted

Table 4. Baseline Agreement (Kappa value)[a] between objective deficits and subjective reports in PD-MCI according to patient's report

a) Memory questions

	Forgetting recent events	p value	Forgetting remote events	p value	Forgetting names	p value	Forgetting appointments	p value	Forgetting medications	p value	Firgetting where objects are placed	p value
Memory	0.028	0.786	0.028	0.786	0.166	0.132	0	NA	0.067	0.317	0.133	0.183
Attention	*0.324*	*0.014*	0.099	0.456	0.694	0.052	0	NA	-0.115	0.310	0.125	0.345
Executive	0.006	0.917	0.006	0.917	0.027	0.684	0	NA	0.035	0.310	-0.004	0.951
Language	0.008	0.951	0.008	0.951	- 0.139	0.288	0	NA	-0.111	0.452	-0.091	0.49
Visuospatial	*- 0.169*	*0.018*	-0.006	0.936	**- 0.02**	**0.01**	0	NA	0.052	0.215	-0.020	0.771

b) Attention questions

	Trouble sustaining attention	p value	Trouble listening well	p value	Easily distracted	p value
Memory	*-0.141*	*0.035*	0.135	0.093	0.102	0.080
Attention	0.183	0.107	0.115	0.357	- 0.090	0.384
Executive	0.035	0.310	0.055	0.205	-0.019	0.527
Language	0.047	0.684	-0.08	0.952	-0.088	0.412
Visuospatial	-0.047	0.265	0.03	0.57	0.039	0.288

c) Executive function questions

	Trouble finishing tasks	p value	Trouble sequencing steps	p value	Poorly organized/ unable to plan	p value

Memory	-0.108	0.208	-0.001	0.98	-0.001	0.98
Attention	0.346	0.007	0.1	0.263	0.1	0.352
Executive	0.065	0.167	0.017	0.481	-0.027	0.263
Language	-0.031	0.809	-0.062	0.507	-0.062	0.507
Visuospatial	-0.008	0.885	-0.023	0.439	-0.023	0.439

d) Language questions

	Trouble naming	**p value**	**Rambling**	**p value**	**Trouble understanding conversations**	**p value**	**Trouble understanding what is read**	**p value**
Memory	*0.236*	*0.022*	0.101	0.173	0.068	0.157	0.100	0.246
Attention	-0.125	0.340	0.005	0.967	-0.063	0.481	0.085	0.507
Executive	-0.045	0.456	-0.002	0.967	0.017	0.481	0.065	0.167
Language	-0.108	0.412	0.019	0.88	-0.062	0.507	-0.031	0.809
Visuospatial	-0.060	0.400	-0.016	0.737	0.026	0.390	-0.060	0.289

e) Non-verbal questions

	Getting lost	**p value**	**Finding multiple step activities confusing**	**p value**	**Dressing confusion**	**p value**
Memory	0	NA	0.033	0.574	0	NA
Attention	0	NA	0.066	0.527	0	NA
Executive	0	NA	0.026	0.384	0	NA
Language	0	NA	-0.088	0.412	0	NA
Visuospatial	0	NA	0.039	0.288	0	NA

NA: Non admitted (no patients complained about it)

Table 5. Baseline Agreement[a] between objective deficits and subjective reports according to close contacts in PD-MCI patients

a) Memory questions

	Forgetting recent events	p value	Forgetting remote events	p value	Forgetting names	p value	Forgetting appointments	p value	Forgetting medications	p value	Firgetting where objects are placed	p value
Memory	0.064	0.478	0.099	0.302	-0.179	0.061	0.101	0.173	0.135	0.093	0.095	0.410
Attention	*0.309*	*0.018*	-0.089	0.274	*0.274*	*0.037*	0.147	0.219	-0.022	0.863	0.01	0.936
Executive	0.026	0.599	-0.013	0.809	-0.013	0.809	0.045	0.252	0.007	0.863	-0.006	0.936
Language	-0.053	0.686	-0.199	0.132	-0.199	0.132	-0.132	0.280	-0.152	0.232	-0.165	0.197
Visuospatial	-0.047	0.438	0.020	0.761	-0.133	0.602	0.066	0.162	0.030	0.570	0.054	0.518

b) Attention questions

	Trouble sustaining attention	p value	Trouble listening well	p value	Easily distracted	p value
Memory	0.064	0.478	-0.004	0.964	-0.142	0.076
Attention	-0.068	0.599	**0.387**	**0.002**	**0.387**	**0.002**
Executive	-0.022	0.659	0.007	0.863	0.007	0.863
Language	-0.185	0.159	-0.152	0.232	-0.152	0.232
Visuospatial	0.006	0.927	0.030	0.570	-0.073	0.164

c) Executive function questions

	Trouble finishing tasks	p value	Trouble sequencing steps	p value	Poorly organized/ unable to plan	p value
Memory	0.032	0.669	0	NA	-0.004	0.964
Attention	0.147	0.219	0	NA	0.251	0.044
Executive	0.045	0.252	0	NA	0.055	0.205
Language	-0.132	0.28	0	NA	-0.152	0.232
Visuospatial	-0.085	0.073	0	NA	-0.022	0.680

d) Language questions

	Trouble naming	p value	Rambling	p value	Trouble understanding conversations	p value	Trouble understanding what is read	p value
Memory	0.029	0.760	-0.073	0.363	0.067	0.317	0.068	0.157
Attention	0.153	0.245	0.115	0.357	-0.115	0.310	-0.063	0.481
Executive	0.036	0.498	0.055	0.205	-0.01	0.764	0.017	0.481
Language	0.053	0.688	-0.152	0.232	-0.111	0.339	-0.062	0.507
Visuospatial	-0.086	0.178	0.081	0.122	0.003	0.951	-0.023	0.439

e) Non-verbal questions

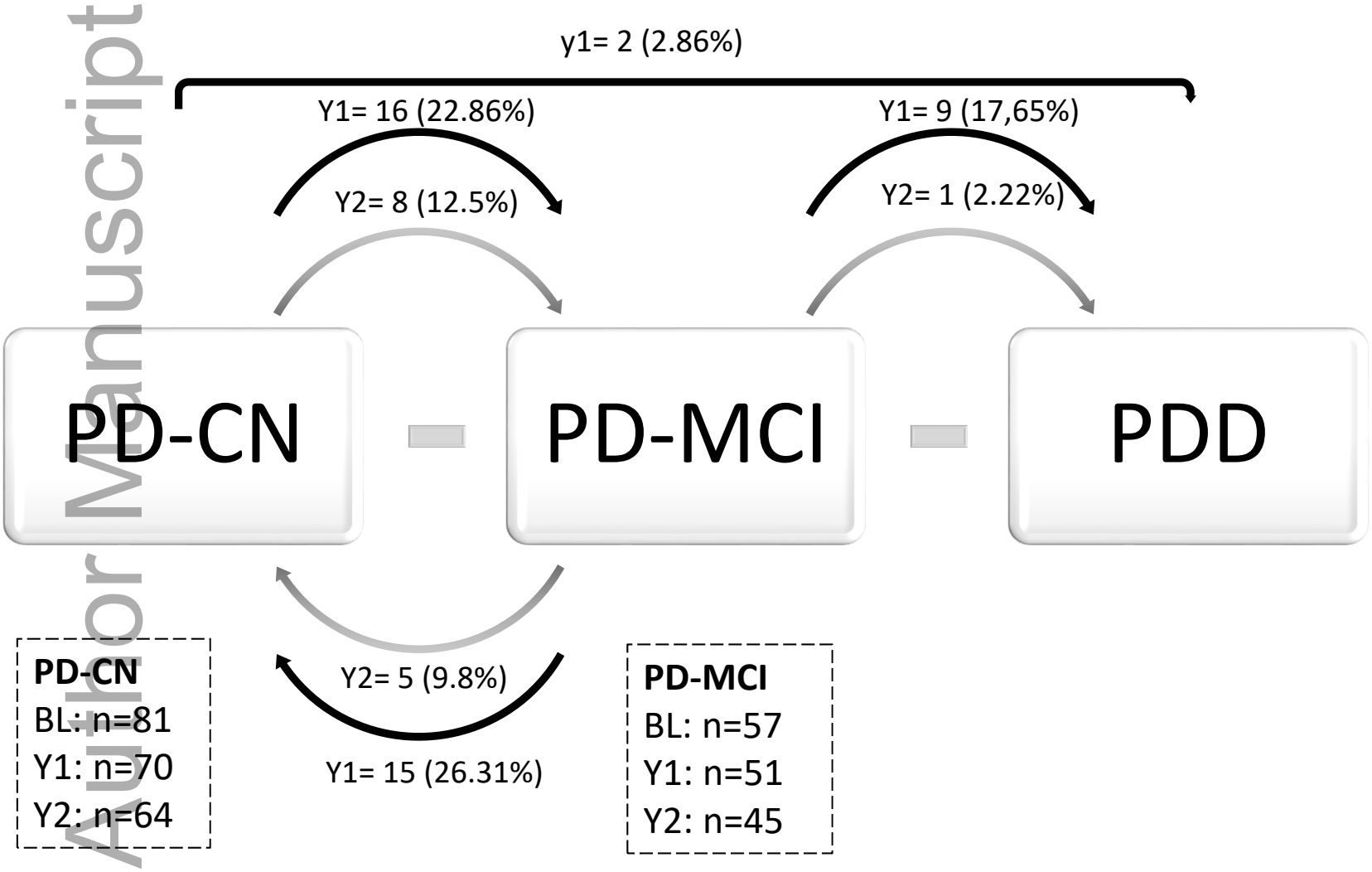
	Getting lost	p value	Finding multiple step activities confusing	p value	Dressing confusion	p value
Memory	0	NR	-0.002	0.971	0.034	0.322
Attention	0	NR	0.034	0.764	-0.033	0.622
Executive	0	NR	-0.01	0.764	0.009	0.622
Language	0	NR	-0.111	0.339	-0.032	0.642
Visuospatial	0	NR	0.052	0.215	0.013	0.547

NA: Not reported (no close contacts reported this problem)

* The threshold for statistical significance considering correction for multiple comparisons =
a) Memory= 0.01, b) attention= 0.017, c) executive function= 0.017, 4) language= 0.0125, 5) non-verbal= 0.017.
Statistically significant results are shown in bold type
Statistically significant results before multiple comparisons correction are shown in italics.

[a] agreement according to presence or absence of any complaint (kappa value)

Figure 1. Graphical summary of conversion and reversion rates at year 1 and 2 of follow up according to PD cognitive diagnosis at baseline.



Total PD-CN converters to PD-MCI/PDD after 2 years: 13
Total PD-MCI converters to PDD after 2 years: 10