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Authors

Nunes, Paula Villela
Schwarzer, Monise Caroline
Leite, Renata Elaine Paraizo
et al.

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Neuropsychiatric Inventory in Community-Dwelling Older Adults with Mild Cognitive Impairment and Dementia

Paula Villela Nunes[a,c,*], **Monise Caroline Schwarzer**[c], **Renata Elaine Paraizo Leite**[a], **Renata Eloah de Lucena Ferretti-Rebustini**[a,d], **Carlos Augusto Pasqualucci**[a], **Ricardo Nitrini**[a], **Roberta Diehl Rodriguez**[a], **Camila Fernandes Nascimento**[a], **Katia Cristina de Oliveira**[a], **Lea Tenenholz Grinberg**[a,b], **Wilson Jacob-Filho**[a], **Beny Lafer**[a], and **Claudia Kimie Suemoto**[a]

[a]Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, SP, Brazil

[b]Memory and Aging Center University of California, San Francisco, USA

[c]Faculdade de Medicina de Jundiai, Brazil

[d]Escola de Enfermagem, Universidade de Sao Paulo, Sao Paulo, SP, Brazil

Abstract

Background—Behavioral and psychological symptoms (BPSD) can be a prodrome of dementia, and the Neuropsychiatric Inventory (NPI) is widely used for BPSD evaluation.

Objective—To compare the prevalence of BPSD according to cognitive status, and to determine NPI cutoffs that best discern individuals with mild cognitive impairment (MCI) and dementia from those without dementia.

Methods—We included 1,565 participants (mean age = 72.7 ± 12.2 years, 48% male). BPSD and cognitive status were assessed with the NPI and the Clinical Dementia Rating (CDR). We used multivariable logistic regression models to investigate the association of BPSD with cognitive status. The area under the curve (AUC) was used to assess model discrimination, and to determine the best NPI cutoff for MCI and dementia.

Results—Participants were cognitively normal (CDR = 0; n = 1,062), MCI (CDR = 0.5; n = 145), or dementia (CDR ≥ 1.0, n = 358). NPI symptoms were more frequent in dementia and MCI when compared to cognitively normal. Higher odds for delusions, hallucinations, disinhibition, and psychomotor alterations were found among participants with dementia and MCI than in those who were cognitively normal. The best NPI cutoff to discern participants with dementia from those cognitively normal was 11 (AUC = 0.755). Poor discrimination (AUC = 0.563) was found for the comparison of MCI and those cognitively normal.

Conclusions—We found an increase in BPSD frequencies across the continuum of cognitive impairment. BPSD severity and frequency in MCI was more similar to individuals cognitively

*Correspondence to: Paula Villela Nunes, PROMAN – r. Dr. Ovídio Pires de Campos, 785 – São Paulo, SP 01060-970, Brazil. Tel.: +55 11 98404 8685; Fax: +55 11 3085 2254; paula@formato.com.br.

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SUPPLEMENTARY MATERIAL

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normal than with dementia. NPI scores ≥ to 11 in individuals with no diagnosis of dementia can support the decision for further investigation of dementia.

Keywords

Behavioral and psychological symptoms; dementia; mild cognitive impairment; Neuropsychiatric Inventory

INTRODUCTION

Behavioral and psychological symptoms of dementia (BPSD) not only induce significant disability in demented patients, but they also increase caregiver stress [1, 2]. There is a continued increase of BPSD frequency from non-demented individuals to those with the various forms of dementia [3]. BPSD can appear before cognitive alterations or during the course of the illness, and they increase in parallel to dementia severity. Evidence suggest that BPSD may act as a prodrome of a dementia syndrome. For instance, BPSD were identified at higher prevalence in individuals who later developed dementia, measured by the Clinical Dementia Rating scale, (CDR), compared to those that remained cognitively normal [4]. Additionally, in patients with mild cognitive impairment, the risk of cognitive decline was increased in those with greater number and more intense BPSD [5].

The terms “cognitive impairment, no dementia” (CIND) and “mild cognitive impairment” (MCI) have been used to describe individuals that may be in the prodromal stages of dementia [6]. There is a growing interest in identifying predictors of a higher risk of transition from CIND/MCI stages to dementia in order to target specific treatments earlier in the course of the disease [7]. Therefore, knowledge about BPSD frequency along the continuum from normal cognition to dementia can help early detection and proper symptom management.

The Neuropsychiatric Inventory (NPI) is a widely used scale that evaluates 12 BPSD commonly found in dementia. It is a valid and reliable instrument for examining behavior and mood symptoms in people with dementia [8]. It is considered one of the most useful outcome measures for behavior and mood symptoms in people with dementia, and although initially designed to screen demented individuals, it has been used to evaluate patients with psychotic, affective, and other neurological disorders [9]. Very few studies that have investigated the properties of the NPI in patients with MCI [10]. Moreover, so far, no study has proposed an NPI cutoff that discern MCI and dementia. In light of that, we aimed to compare the prevalence of BPSD according to cognitive status, and to determine NPI cutoffs that best discern individuals with MCI and dementia from those without dementia.

MATERIALS AND METHODS

A cross-sectional study was conducted in deceased subjects submitted to autopsy at the Sao Paulo Autopsy Service (SPAS) between 2004 and 2016. In Brazil, autopsy is mandatory for all individuals whose cause of death was not identified before death. SPAS is a community-based general autopsy service responsible for issuing death certificates in such cases within the city of Sao Paulo, Brazil.

Participants

Subjects were participants of the Brazilian Biobank for Aging Studies, formerly known as Brain Bank of the Brazilian Aging Brain Study Group (BBBABSG) from 2004 to 2016. Methodological procedures of the BB-BABSG have been described elsewhere [11–13]. Inclusion criteria were age 50 years and older, and non-traumatic cause of death. Cases with no reliable informant, medical history of advanced chronic disease, or prolonged agonal state were excluded. In addition, subjects with major cerebral lesions, including hemorrhagic stroke and cerebral tumors, were excluded from the BB-BABSG because immediate brain examination is required to confirm the cause of death. A knowledgeable informant was invited to participate in the study. A knowledgeable informant was a close family member or caregiver that had at least one weekly contact with the deceased in the last six months prior to death and was able to recount and provide details of the deceased's health information. Sociodemographic information was collected using two sources. Age at death and sex were retrieved from the government-issued national identification, named general registration (GR). The GR is necessary for almost all aspects of citizen life, including access to public health system, and is one of the most reliable sources of information on age and sex. The next of kin answered a structured interview, which contains deceased's information on: number of years of formal education, frequency of contact with the informant, and race. Race was classified in: white, black, brown, and other races (i.e., Asian and Brazilian Indian) [13]. Subjects were included after the study procedures had been explained to the family members and they had agreed to participate by signing an informed consent form. The local ethics committee approved the research protocol.

Clinical postmortem evaluation

Clinical evaluation consisted of assessment of the deceased's clinical and functional status in the three months prior to death. Information was obtained with the informant. A validated semi-structured clinical interview [14] assessed demographics (age, gender, and formal educational attainment), conditions related to death, past medical history (clinical and surgical), treatments, smoking habits, alcohol consumption, physical activity, functional status, neuropsychiatric symptoms, and cognitive performance. Clinical medical history was assessed in detail during the interview with the informant, including history of hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, heart failure, and stroke, among other clinical data.

Neuropsychiatric symptoms in the three months prior to death were further assessed with the NPI. The NPI measures the frequency and the severity of neuropsychiatric symptoms. It evaluated 12 symptoms: delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, psychomotor alterations, sleep change, and eating change. It is a structured interview applied to an informant knowledgeable about the participant, and it focuses on observable symptoms and behaviors. If any of these symptoms are present, they are rated on a 4-point frequency scale and on a separate 3-point severity scale. The product of the frequency and severity scales within each domain produces a total domain score, which ranges from 0 to 12. Individual domain scores are summed to produce a total NPI score (range: 0–144) [8, 10]. The rates for any symptom (NPI > 0), and for moderate symptoms (NPI ≥ 4) for each item were used [7, 10]. We used the Informant Questionnaire

on Cognitive Decline in the Elderly (IQCODE) [15], and the informant part of the Clinical Dementia Rating scale (CDR) [16] validated for postmortem use [14] to evaluate cognitive performance. Functional status was accessed with the Index of Katz for the assessment of Activities of Daily Living (ADL) [17], and Lawton and Brody Instrumental Activities of Daily Living (IADL) [18]. Participants were divided into three groups according to the CDR: those with CDR = 0 were named *cognitively normal*, those with CDR = 0.5 were named *MCI*, and those with CDR ≥ 1.0 were named *dementia*, according to previous publications [4]. Cognitive and functional differences between the groups were further confirmed with the IQCODE, ADL, and IADL.

Statistical analysis

To compare participants in the cognitively normal, MCI, and dementia groups, we used one-way ANOVA for quantitative variables, and the chi-square test for categorical variables, followed by a non-parametric test for trend across ordered groups [19]. We used multivariable logistic regression models, adjusted for age, gender, race, and education to compare the frequency of each of the 12 NPI items in participants in the MCI or dementia groups to that of participants in the cognitively normal group. Education was operationalized as a linear variable of years of education. We used linear models adjusted for the same variables to examine the association between NPI total score and cognitive status. In order to determine the better NPI cutoff to discriminate participants in the cognitively normal or MCI groups, and participants in the cognitively normal and dementia groups, we generated receiver operator characteristics (ROC) curves and used the Youden index [20], which gives the cutoff score with the best balance between sensitivity and specificity. Finally, we used the non-parametric method described by DeLong et al. [21] for the comparison between the AUC for the 12 NPI items scores >0 and the AUC for the NPI items scores ≥ 4 to discriminate participants in the MCI group from those in the cognitively normal group, and to discriminate participants in the cognitively normal and dementia groups. The level of significance was set at 0.05 in two-tailed tests. The software Statistical Package for the Social Sciences (SPSS) version 20.0 and Stata 13.0 (StataCorp, College Station, TX) was used to perform the statistical analyses.

RESULTS

From 2004 to 2016, we collected data from 1,565 individuals; 48.1% were male, and their mean age was 72.7 ± 12.2 years old. Regarding the dementia status, 1,062 older adults had CDR = 0 and classified in the cognitively normal group; 145 had CDR = 0.5 and were in MCI group, and the remaining 358 had CDR ≥ 1.0 and were in the dementia group. Informants were77.8% offsprings (son or grandson), 9.3% spouse, 12.8% other relatives (e.g., brother, sister, nephew, brother-in-law), and 0.2% formal caregivers. They had on average 5 years of formal schooling. No differences on the scores of the NPI were found according to the type of informant. We did not find a correlation between education and NPI scores in this sample. Table 1 shows the comparison of demographics and clinical variables across the continuum of cognitively normal, MCI, and dementia. As expected, there was an increase in age, in the scores of the IQCODE, and in the frequency of physical inactivity from the cognitively normal to the dementia groups. There was also a decrease in the

frequency of men, in the scores of the scales of ADL and IADL, and in the current use of tobacco and alcohol across the continuum of cognitive impairment of participants of the cognitively normal group to those in the MCI and dementia groups. No trend was observed in ethnicity, presence of hypertension or diabetes.

Table 2 shows the prevalence of each of the 12 NPI items by dementia status for any symptom (NPI > 0), and for clinically significant symptoms (NPI ≥ 4). All NPI items were more frequent in participants in the dementia group compared to those in the cognitively normal group. In an adjusted multivariate logistic regression model, delusions, hallucinations, agitation, depression, disinhibition, irritability, and motor behavior were more frequent in the MCI group than in the cognitively normal group. In the dementia group, except for euphoria, all NPI items had a frequency above 20%. In the MCI and cognitively normal groups, only depression, anxiety, sleep and eating changes had a frequency above 20%. Despite depression, anxiety, and appetite changes being highly prevalent in the groups, there was an increase in frequency from the cognitively normal to MCI and dementia groups.

Subjects in the MCI group scored on average 4.2 points higher in the NPI total score than in the cognitively normal group (β = 4.2, 95% CI= 1.5; 6.9, $p = 0.002$), whereas subjects in the dementia group scored on average 17.2 points higher than subjects in the cognitively normal group (β = 17.2, 95% CI= 15.2; 19.1, $p < 0.0001$), using linear regression model adjusted for age, gender, race, and education. In order to discern individuals in the MCI group from those in the cognitively normal group the best NPI total score cutoff was 10 according to the Youden index with an area under the curve (AUC) of 0.563 (95% CI = 0.513–0.614). When we compared the cognitively normal group with dementia, the AUC showed good accuracy (AUC = 0.755, 95% CI = 0.732–0.791), and the best NPI total score cutoff was 11 (Table 3 and Fig. 1). Regarding NPI items, data did not allow cutoffs to be extracted through ROC curves (data available in Supplementary Table 1).

Table 4 shows the performance for each of the 12 NPI items scores > 0 and scores ≥ 4 to discern participants in the MCI group from those in the cognitively normal, and to discern participants in the dementia group from those in the group cognitively normal group. None of the NPI items alone was satisfactory to distinguish the MCI group from those in the cognitively normal group. The AUC for any symptom (NPI > 0) was similar to the AUC for moderate symptoms (NPI ≥ 4). When comparing dementia with cognitively normal groups, a score greater than 0 had better distinction than a score ≥ 4: delusions ($p = 0.0003$), hallucinations ($p < 0.0001$), agitation ($p = 0.002$), and disinhibition ($p = 0.0001$).

DISCUSSION

This is the first study that compares BPSD in the same large community sample of individuals cognitively normal (and in this study without MCI), MCI, and dementia using the NPI. An increase in BPSD was found across the continuum of cognitive impairment from cognitively normal to dementia. The clinical neuropsychological profile of MCI subjects was closer to that of individuals with normal cognition than to that of individuals with dementia. Comparing individuals with dementia and in the cognitively normal group,

the NPI had good accuracy and a cutoff of 11. The distinction was poor for the comparison of MCI subjects with individuals in the cognitively normal group, and the NPI cutoff was 10. Unlike scales traditionally used for dementia screening (e.g., the Mini-mental State Examination and the Montreal Cognitive Assessment), which have well-established cutoffs to discern dementia, as far as we are concerned, this is the first time that a cutoff is proposed for the NPI. The difficulty in establishing a cutoff for discerning MCI from cognitively normal individuals may be indicative of how close these two conditions are with respect to BPSD.

Despite not being the core symptom for the diagnosis of MCI or dementia, BPSD can be a risk factor for dementia [22]. The association of BPSD and dementia was also found in previous studies, especially when BPSD are more intense [7] or more frequent [10]. Moreover, early presence of NPI symptoms in cognitively normal patients, who subsequently developed MCI or dementia, has been shown in large longitudinal studies [4, 5]. In addition, more intense BPSD evaluated by NPI in patients with MCI were associated with greater risk of developing dementia [5,7]. Therefore, an NPI cutoff could help health professionals to identify individuals in who high scores may justify further assessment for MCI or dementia diagnosis. Moreover, individuals with high scores in the NPI may benefit from a careful cognitive follow-up.

The rates for any symptom (NPI > 0), and for moderate symptoms (NPI ≥ 4) by each item were used according to previous publications [7, 10]. The presence of moderate symptoms was not superior to any symptom in all domains for the discrimination of MCI and dementia. Therefore, even if not quantified in terms of frequency and severity, the presence of neuropsychiatric symptoms may be enough to draw health providers' or clinicians' attention. When comparing individuals with dementia to those without dementia, all NPI items were more prevalent in the dementia group, with less robust data for anxiety symptoms, which were very prevalent in all groups in our sample. Symptoms that best differentiated individuals with dementia and in the cognitively normal group were delusions, hallucinations, agitation, and disinhibition as shown in the AUC analyses. Similar results were found in a prospective study of 2,416 individuals with dementia and no dementia [4]. Interestingly, depression scores and other behavioral symptoms evaluated by the NPI items were also shown to worsen faster among individuals with preclinical AD dementia at baseline defined by CSF biomarkers [23].

When comparing the NPI of individuals with MCI with that of individuals in the cognitively normal group, in MCI a greater prevalence was found for delusions, hallucinations, agitation, depression, disinhibition, irritability, and psychomotor alterations, but the values of the odds were smaller than those found in the comparison between dementia and the cognitively normal group. No single symptom represented by the items of the NPI was enough to differentiate the MCI and in the cognitively normal group, analyzed through the AUC.

Depression was one of the most common NPI symptoms present in the MCI group, which is in accordance with the literature [10, 24–26]. In the cognitively normal group, depression was also highly prevalent, as were anxiety symptoms. Symptoms most prevalent in our

group of individuals with dementia (present in more than 35% of the sample) were hallucinations, agitation, depression, apathy, sleep, and eating changes. Despite that, since depression is considered either a risk factor or a prodrome for cognitive decline or dementia [27, 28], even depression alone should be a warning sign for the possibility of dementia, especially if refractory to treatments. Euphoria was by far the NPI symptom least present, as seen in prospective follow-ups of patients with dementia [29]. The importance of apathy is in accordance with previous publications [3, 5, 10, 24, 29–31] as are those BPSDs related to psychosis and hyperactivity (delusion, hallucination, disinhibition and motor behavior) [3]. According to previous longitudinal follow-ups, BPSDs can rapidly get more intense and dysfunctional in dementia [29, 31]; therefore, investigation of such symptoms during health care appointments should be warranted.

Strengths of our study include a large sample size from community-based older adults, and a diverse population in terms of ethnicity and educational background from a country with low average income. Additionally, although samples were heterogeneous in terms of clinical variables, we presented adjusted analyses for the association between NPI and cognitive status. Yet, our study also has several limitations that have to be taken into consideration. Our study is a random subsample selected from individuals that were referred for autopsy because we did not collect cases 24 hours a day seven days a week. In addition, the cross-sectional and observational nature of the study did not allow for the examination of factors related to the temporal transition from normal cognition to MCI and dementia. Moreover, the use of informant-reported data retrospectively collected is a concern, as informants can be unaware of some treatments and disorders of the deceased. In order to overcome these limitations, the clinical interview with informants used in this study was validated in clinical settings [14].

The CDR used in this study is a screening tool for assessing cognitive function, so it presents limitations when cognitive function is assessed clinically, especially for the screening of MCI. In large longitudinal studies, CDR = 0.5 is used as a parameter for MCI [5, 7], validated by scores ≤ 1.5 SD in neuropsychological evaluation adjusted for age and education. However, in our sample we used CDR associated with other functional scales, but not with formal neuropsychological evaluation. Therefore, it is possible that our sample with CDR = 0.5 did not represent all subjects that could be diagnosed whether a complete neuropsychological evaluation was available. Despite of that, the clinical, functional and cognitive profile of our MCI sample shown in Table 1 was between no dementia and dementia as expected. We did not follow participants during life, and clinical variables were evaluated postmortem through an interview with an informant. To increase the reliability of these data, we included only participants who had at least weekly contact with the informant and excluded individuals when the informant provided conflicting information during the clinical interview. In addition, we have shown that the postmortem cognitive evaluation had a sensitivity of 87% and specificity of 84% for the clinical diagnosis of dementia [14]. CDR was designed to be applied to both the patient and his/her informant. Since we did not follow participants during life, we only applied the CDR to the informant. Despite of these limitations, the CDR is still widely used in population-based studies of dementia [4].

Another limitation of our study was that we did not analyze the BPSD by dementia etiology. Each dementia cause is associated with a specific BPSD profile. For example, visual hallucinations often occur early in Lewy body dementia, but usually later and in more severe stages of Alzheimer's disease [32]. Disinhibition is common in frontotemporal dementia [32], while usually uncommon in other causes of dementia. Additionally, some studies found only minor differences in the prevalence of behavioral disturbances in Alzheimer's disease and vascular dementia [33], while others could find important differences [34]. As an example, frontotemporal dementia is an insidious neurodegenerative syndrome characterized by progressive deficits in behavior, executive function, and language. The disorder is the third most common form of neurodegenerative disease across all age groups, after Alzheimer's disease and dementia with Lewy bodies, and it is a leading cause of early-onset dementia [35]. The fact that most scales for staging dementia were developed based on symptoms of Alzheimer's disease, and they are potentially less sensitive to the progression seen in other dementias deserves some attention. To overcome this issue, more recently language and behavior domains, which are often impaired in frontotemporal dementia, were included in a new version of the CDR, forming the Clinical Dementia Rating Scale for Frontotemporal Lobar Degeneration (CDR-FTLD) [36]. Given the need to develop specific instruments for staging typical symptoms of frontotemporal dementia variants, another scale, the Frontotemporal Dementia Rating Scale (FTD-FRS), was also developed [37]. The validity and reliability of FTD-FRS Brazilian version was recently published [38], allowing its use in future studies. Another limitation of the present study was that we could not examine the effect of informant's distress on NPI scores because the NPI Distress (NPI-D) scale was not available for all the sample. Despite these limitations, other studies with the same methodology for collecting information have been published [4, 13,39, 40].

The main findings of this study were that some symptoms, such as delusion, hallucination, disinhibition, and psychomotor alterations, are particularly useful as warning signs for possible progression to cognitive impairment and, more specifically, to dementia. We found that the best NPI cutoff to discern participants with dementia and the cognitively normal group was 11. Scores above this value in individuals without the diagnosis of dementia can, according to clinical judgment, support the decision for further investigation of cognitive impairment. Finally, a better comprehension and detection of BPSD is essential, since quality of life in dementia is closely related to these symptoms, sometimes more so than with cognitive scores themselves [41].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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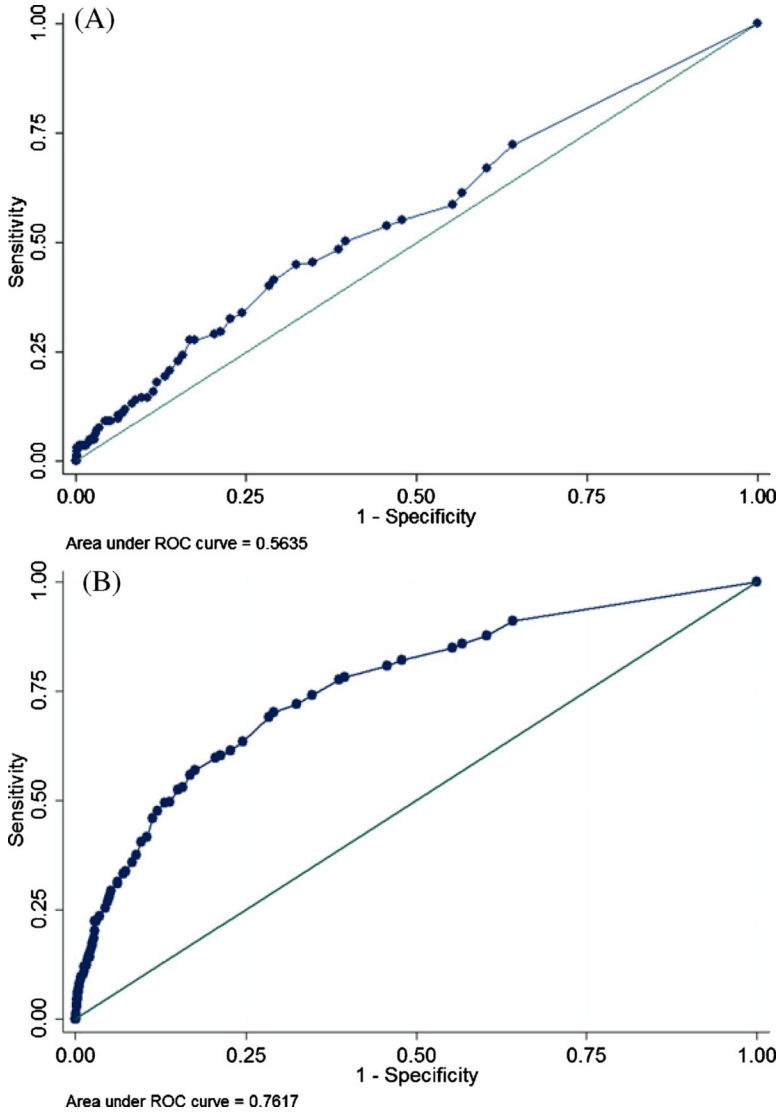

Fig. 1.

ROC curve for the comparison between (A) individuals with mild cognitive impairment (MCI) and those in the cognitively normal group, and (B) individuals with dementia and those in the cognitively normal group.

Table 1

Study population characteristics according to cognitive status (n = 1,565)

	Cognitively normal (n = 1,062)	MCI (n = 145)	Dementia (n = 358)	p
Age (y), mean (SD) *	70.2 (12.3)	74.2 (10.7)	79.7 (9.4)	<**0.001**
Male, n (%) †	552 (52.0)	66 (45.5)	135 (37.7)	<**0.001**
White race, n (%) †	713 (67.2)	94 (64.8)	252 (70.4)	0.32
Education (y), mean (SD) *	4.9 (3.9)	3.6 (2.7)	3.3 (3.4)	<**0.001**
IQCODE, mean (SD) *	3.0 (0.1)	3.3 (0.2)	4.3 (0.6)	<**0.001**
ADL, mean (SD) *	5.6 (1.2)	5.1 (1.6)	2.2 (2.2)	<**0.001**
IADL, mean (SD) *	6.8 (2.1)	5.2 (2.6)	1.1 (1.8)	<**0.001**
Hypertension, n (%) †	686 (65.3)	104 (74.8)	211 (59.9)	0.17
Diabetes, n (%) †	280 (26.7)	48 (34.3)	102(29.1)	0.24
Physical inactivity, n (%) †	427 (48.5)	56 (67.5)	198 (82.2)	<**0.001**
Current smoking, n (%) †	374 (37.3)	33 (27.5)	50 (15.7)	<**0.001**
Current alcohol use, n (%) †	159 (15.9)	16(13.3)	23 (7.3)	**0.04**

MCI, mild cognitive impairment; SD, standard deviation; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living.

* one way ANOVA

† chi-square test followed by a non-parametric test for trend across ordered groups.

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Table 2

Association between each of the 12 Neuropsychiatrie Inventory (NPI) item scores and cognitive status (n = 1,565)

	Cognitively normal (n = 1,062)	MCI (n = 145)	Dementia (n = 358)	MCI × Cognitively normal OR (95% CI)	p^*	Dementia × Cognitively normal OR (95% CI)	p^*
Delusions							
Any symptom (NPI > 0)	3.6%	8.2%	26.1%	2.72 (1.32–5.62)	**0.007**	11.60 (7.12–18.9)	**<0.0001**
Moderate symptoms (NPI ≥ 4)	2.1%	3.7%	19.5%	2.22 (0.80–6.20)	0.13	15.47 (8.36–28.61)	**<0.0001**
Hallucinations							
Any symptom (NPI > 0)	4.3%	11.2%	38.0%	2.97 (1.57–5.62)	**0.001**	13.98 (9.09–21.52)	**<0.0001**
Moderate symptoms (NPI ≥ 4)	2.0%	3.0%	27.7%	1.58(0.52–4.81)	0.42	18.13 (10.24–32.11)	**<0.0001**
Agitation							
Any symptom (NPI > 0)	11.6%	17.9%	41.9%	1.84 (1.12–3.03)	**0.02**	6.97 (4.96–9.80)	**<0.0001**
Moderate symptoms (NPI ≥ 4)	7.6%	14.2%	32.5%	2.10(1.21–3.66)	**0.008**	6.66 (4.57–9.69)	**<0.0001**
Depression							
Any symptom (NPI > 0)	26.0%	34.3%	39.3%	1.56(1.05–2.32)	**0.03**	2.15 (1.61–2.88)	**<0.0001**
Moderate symptoms (NPI ≥ 4)	19.4%	28.4%	31.7%	1.73 (1.14–2.63)	**0.01**	2.28 (1.67–3.11)	**<0.0001**
Anxiety							
Any symptom (NPI > 0)	23.9%	28.4%	29.0%	1.35 (0.89–2.04)	0.16	1.38 (1.02–1.88)	**0.04**
Moderate symptoms (NPI ≥ 4)	15.7%	18.7%	22.3%	1.34 (0.83–2.17)	0.23	1.72(1.21–2.42)	**0.002**
Euphoria							
Any symptom (NPI > 0)	1.9%	2.2%	6.7%	1.38 (0.39–4.88)	0.62	5.01 (2.39–10.50)	**<0.0001**
Moderate symptoms (NPI ≥ 4)	0.6%	1.5%	4.3%	3.19 (0.59–17.14)	0.18	10.83 (3.42–34.34)	**<0.0001**
Apathy							
Any symptom (NPI > 0)	13.3%	18.7%	39.2%	1.53 (0.94–2.47)	0.09	4.43 (3.21–6.12)	**<0.0001**
Moderate symptoms (NPI ≥ 4)	8.6%	11.9%	33.4%	1.47 (0.82–2.63)	0.19	5.83 (4.05–8.39)	**<0.0001**
Disinhibition							
Any symptom (NPI > 0)	1.5%	6.7%	22.3%	5.45 (2.25–13.22)	**<0.0001**	24.96(12.81–48.65)	**<0.0001**
Moderate symptoms (NPI ≥ 4)	0.6%	5.2%	16.2%	10.87 (3.34–35.34)	**<0.0001**	45.20 (16.89–120.96)	**<0.0001**
Irritability							
Any symptom (NPI > 0)	11.7%	24.6%	28.0%	2.71 (1.72–4.27)	**<0.0001**	3.51 (2.48–4.98)	**<0.0001**
Moderate symptoms (NPI ≥ 4)	6.7%	17.2%	20.7%	3.25 (1.90–5.56)	**<0.0001**	4.81 (3.16–7.32)	**<0.0001**
Psychomotor alterations							

	Cognitively normal (*n* = 1,062)	MCI (*n* = 145)	Dementia (*n* = 358)	MCI × Cognitively normal OR (95% CI)	*p**	Dementia × Cognitively normal OR (95% CI)	*p**
Any symptom (NPI > 0)	2.9%	6.7%	22.6%	2.47(1.12–5.46)	**0.03**	9.67 (5.79–16.15)	**<0.0001**
Moderate symptoms (NPI ≥ 4)	1.5%	2.2%	19.2%	1.53 (0.43–5.50)	0.51	15.36 (7.97–29.62)	**<0.0001**
Sleep change							
Any symptom (NPI > 0)	19.4%	21.6%	36.3%	1.20(0.77–1.89)	0.41	2.61 (1.92–3.54)	**<0.0001**
Moderate symptoms (NPI ≥ 4)	16.3%	17.9%	32.0%	1.18 (0.73–1.91)	0.50	2.68 (1.95–3.69)	**<0.0001**
Appetite change							
Any symptom (NPI > 0)	27.5%	26.3%	49.1%	0.90(0.60–1.37)	0.64	2.30(1.74–3.05)	**<0.0001**
Moderate symptoms (NPI ≥ 4)	21.9%	15.8%	41.5%	0.64 (0.39–1.06)	0.08	2.40(1.79–3.21)	**<0.0001**

*Multivariable logistic regression, adjusted for age, gender, race, and education. Reference: subjects in the cognitively normal group.

Table 3

Total NPI score cutoff to discriminate among subjects cognitively normal, with MCI, and with dementia (n = 1,565)

	Sensitivity	Specificity	AUC (CI 95%)	Optimal NPI cutoff*
MCI versus Cognitively normal	0.448	0.676	0.563 (0.513–0.614)	10
Dementia versus Cognitively normal	0.701	0.709	0.762 (0.732–0.791)	11

*defined by the Youden Index.

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Table 4

Accuracy for each of the 12 Neuropsychiatrie Inventory (NPI) item scores and cognitive status (n = 1,565)

	MCI × Cognitively normal		Dementia × Cognitively normal	
	AUC (95% CI)	p^*	AUC (95% CI)	$p^\dagger$
Delusions		0.11		**0.0003**
Any symptom (NPI > 0)	0.523 (0.499–0.547)		0.613 (0.588–0.637)	
Moderate symptoms (NPI ≥ 4)	0.508 (0.491–0.525)		0.587 (0.565–0.609)	
Hallucinations		0.01		**<0.0001**
Any symptom (NPI > 0)	0.535 (0.507–0.562)		0.669 (0.641–0.696)	
Moderate symptoms (NPI ≥ 4)	0.505 (0.490–0.520)		0.629 (0.603–0.653)	
Agitation		0.91		**0.002**
Any symptom (NPI > 0)	0.531 (0.497–0.566)		0.652 (0623–0681)	
Moderate symptoms (NPI ≥ 4)	0.533 (0.502–0.564)		0.624 (0.598–0.651)	
Depression		0.78		0.54
Any symptom (NPI > 0)	0.541 (0.499–0.584)		0.567 (0.536–0.597)	
Moderate symptoms (NPI > 4)	0.545 (0.504–0.585)		0.561 (0.533–0.590)	
Anxiety		0.59		0.36
Any symptom (NPI > 0)	0.522 (0.481–0.563)		0.525 (0.497–0.554)	
Moderate symptoms (NPI ≥ 4)	0.515 (0.480–0.550)		0.533 (0.507–0.559)	
Euphoria		0.53		0.21
Any symptom (NPI > 0)	0.502 (0.489–0.515)		0.524 (0.510–0.539)	
Moderate symptoms (NPI ≥ 4)	0.505 (0.494–0.515)		0.518 (0.507–0.530)	
Apathy		0.39		0.49
Any symptom (NPI > 0)	0.527 (0.492–0.562)		0.630 (0.601–0.658)	
Moderate symptoms (NPI ≥ 4)	0.517(0.488–0.546)		0.624 (0.597–0.651)	
Disinhibition		0.61		**0.0001**
Any symptom (NPI > 0)	0.526 (0.504–0.548)		0.604 (0.581–0.627)	
Moderate symptoms (NPI ≥ 4)	0.523 (0.504–0.542)		0.578 (0.558–0.598)	
Irritability		0.30		0.15
Any symptom (NPI > 0)	0.565 (0.527–0.603)		0.581 (0.555–0.608)	
Moderate symptoms (NPI ≥ 4)	0.552 (0.519–0.585)		0.570 (0.546–0.593)	

	MCI × Cognitively normal		Dementia × Cognitively normal	
	AUC (95% CI)	***p****	**AUC (95% CI)**	***p**†*
Psychomotor alterations		0.09		0.07
Any symptom (NPI > 0)	0.519(0.497–0.541)		0.598 (0.575–0.622)	
Moderate symptoms (NPI ≥ 4)	0.504 (0.490–0.517)		0.589 (0.567–0.610)	
Sleep change		0.73		0.37
Any symptom (NPI > 0)	0.511 (0.473–0.548)		0.584 (0.555–0.613)	
Moderate symptoms (NPI ≥ 4)	0.508 (0.473–0.543)		0.579 (0.550–0.607)	
Appetite change		0.08		0.24
Any symptom (NPI > 0)	0.506 (0.466–0.547)		0.608 (0.577–0.639)	
Moderate symptoms (NPI ≥ 4)	0.530 (0.496–0.564)		0.598 (0.568–0.628)	

*Comparison between AUC NPI score > 0 and AUC NPI score ≥ 4 to discriminate participants with mild cognitive impairment from those in the cognitively normal group, using the non-parametric method described by DeLong et al. (1988).

†Comparison between AUC NPI score > 0 and AUC NPI score ≥ 4 to discriminate participants with dementia from those cognitively normal group, using the non-parametric method described by DeLong et al. (1988).