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Assessing Mild Behavioral Impairment with the Mild Behavioral Impairment-Checklist in People with Mild Cognitive Impairment

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Abstract.
Background: Neuropsychiatric symptoms (NPS) are non-cognitive, behavioral, or psychiatric symptoms, common in mild cognitive impairment (MCI) and associated with a higher risk of dementia. Mild behavioral impairment (MBI) is a validated diagnostic entity, that describes the emergence of later life NPS in pre-dementia states. The Mild Behavioral Impairment Checklist (MBI-C) is the first measure developed to assess MBI.
Objective: To estimate the prevalence of MBI in people with MCI and to study the score distribution, sensitivity, specificity, diagnostic utility of the MBI-C, and its correlations with neuropsychological tests.
Methods: One hundred eleven MCI participants were evaluated with the Questionnaire for Subjective Memory Complaints (QSMC), Mini-Mental State Examination, Cambridge Cognitive Assessment-Revised, Neuropsychiatric Inventory-Questionnaire (NPI-Q), Geriatric Depression Scale-15 items (GDS-15), Lawton and Brody Index, and the MBI-C, which was administered by phone to participants' informants. Descriptive, logistic regression, ROC curve, and bivariate correlations analyses were performed.
Results: MBI diagnosis prevalence was 14.2%. The total MBI-C score differentiated people with MBI at a cutoff-point of 6.5, optimizing sensitivity and specificity. MBI-C total score correlated positively with NPI-Q, QSMC, GDS-15, and Lawton and Brody Index.
Conclusion: The total MBI-C score, obtained by phone administration, is sensitive for detecting MBI in people with MCI. The MBI-C scores indicated that MCI participants had subtle NPS that were correlated to their subjective memory complaints reported by informants, depressive symptoms, and negatively with Instrumental Activities of Daily Living. Further research should be done to clarify the predictive role of NPS in MCI for incident dementia.

Keywords: Behavioral and psychological symptoms of dementia, dementia, mild behavioral impairment, mild cognitive impairment, neuropsychiatric symptoms, preclinical dementia, prodromal dementia

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INTRODUCTION

Neuropsychiatric symptoms in mild cognitive impairment

Neuropsychiatric symptoms (NPS), also known as behavioral and psychological symptoms of dementia (BPSD), are non-cognitive, behavioral, or psychiatric symptoms that include disturbances of mood, perception, and behavior related to a neurocognitive disorder [1].

NPS are associated with greater functional impairment [2], accelerated progression to dementia [3], higher burden of neuropathologic markers of dementia [4], greater caregiver stress [5], and poorer quality of life [6]. NPS are common in mild cognitive impairment (MCI), with prevalence from 35% to 85% [7, 8]. People with MCI and NPS have a greater impairment in global, cognitive, and functional scores compared to those who have MCI without NPS [9]. NPS also increase the likelihood of developing dementia in people with MCI at baseline [3, 10] and thus are important targets for further research in dementia prevention and prognostication.

Mild behavioral impairment diagnosis

To facilitate this further research into NPS and risk of dementia, and make explicit the relationship between NPS and MCI, the NPS Professional Interest Area of the International Society to Advance Alzheimer's Research and Treatment (ISTAART), a subgroup of the Alzheimer's Association (AA), published research diagnostic criteria for Mild Behavioral Impairment (MBI) [11] (Table 1). The ISTAART-AA MBI criteria mandate that NPS be emergent in later life with a minimum six-month duration, to minimize the inclusion of transient and reactive states, and to increase signal detection. Additionally, formal psychiatric illness is an exclusion criterion, and precludes an MBI diagnosis. In this framework then, MBI reflects the neurobehavioral axis of possible predementia risk states, and MCI reflects the neurocognitive axis. Accordingly, symptoms on these axes can emerge together (MCI and MBI), independently (MCI or MBI), or sequentially (MBI before MCI or vice versa) in advance of dementia. MBI is a validated construct. In a 5-year longitudinal study of older adults, MBI had a higher conversion rate to dementia than a psychiatric comparator group consisting of late life psychiatric disorders [12], highlighting the distinction between MBI and late life psychiatric disorders, and the prognostic utility of identifying MBI separately. Thus, detecting the NPS that constitute MBI may aid in earlier detection of dementia at the prodromal phase, in advance of cognitive impairment. ISTAART further operationalized the measurement of MBI with the development of the Mild Behavioral Impairment-Checklist (MBI-C, available at http://www.MBItest.org) [13], a rating scale designed to elicit emergent NPS in a community dwelling, functionally independent, older population, in accordance with the ISTAART-AA MBI criteria. The explicit goal of the MBI-C is MBI case ascertainment, but further validation of its performance is required.

Table 1
ISTAART-AA MBI criteria [11]

1) Changes in behavior or personality observed by patient, informant, or clinician, starting later in life (age ≥50 years) and persisting at least intermittently for ≥6 months. These represent a clear change from the person's usual behavior or personality as evidenced by at least one of the followings:
   a) decreased motivation
   b) affective dysregulation
   c) impulse dyscontrol
   d) social inappropriateness
   e) abnormal thought and perception;
2) Behaviors are of sufficient severity to produce at least minimal impairment in at least one of the following areas:
   a) Interpersonal relationships
   b) Other aspects of social functioning
   c) Ability to perform in the workplace.
   The patient should generally maintain his/her independence of function in daily life, with minimal aids or assistance.
3) Although comorbid conditions may be present, the behavioral or personality changes are not attributable to another current psychiatric disorder, traumatic or general medical causes, or the physiological effects of a substance or medication
4) The patient does not meet criteria for a dementia syndrome. (e.g., Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia, other dementia). MCI can be concurrently diagnosed with MBI.

MBI, mild behavioral impairment; MCI, mild cognitive impairment.

Objectives

To estimate: 1) the prevalence of MBI diagnosis and score distribution in a primary care population with MCI; 2) the sensitivity and specificity of the telephone-administered MBI-C and its utility for diagnosing MBI; and 3) the relationships between NPS, cognitive status, and functional performance in instrumental activities of daily living.

METHODS

Participants

One hundred eleven participants aged ≥50 years with MCI were recruited from patients belonging to all socioeconomic levels attending Public Primary Care Health Centers in Santiago de Compostela (the capital of the autonomous region of Galicia, North-West of Spain) with subjective cognitive complaints (SCC). Participants were excluded if they had: prior diagnosis of depression or other psychiatric disturbances, according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria [14]; prior diagnosis of neurological disease, including probable Alzheimer's disease (AD) or other types of dementia, according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [15] and DMS-5 criteria [14]; previous brain damage or brain surgery; previous chemotherapy; prior diagnosis of diabetes type II; sensory or motor disturbances; and consumption of substances that might affect normal performance of the tasks.

The participants underwent clinical, neurological, and neuropsychological examination conducted respectively by general practitioners, cognitive neurologists, and neuropsychologists specialized in aging and dementia. All assessments included in this study were completed in a period of three weeks for each participant. The Charlson's Comorbidity Index [16] was obtained from the medical history. MCI was diagnosed in accordance with Petersen's [17] criteria revised by Albert et al. [18]: 1) evidence of concern corroborated by an informant about a change in cognition, in comparison with the previous level; 2) evidence of poorer performance in one or more cognitive domains that is greater than expected for the patient's age and educational background; 3) preservation of independence in functional abilities; and 4) non-fulfilment of diagnostic criteria for dementia (NINCDS-ADRDA [15] and DSM-5 criteria [14]).

Study protocol approvals, registrations, and patient consents

The study was approved by the Ethics in Clinical Research Committee of the Galician Government and was carried out in accordance with the Declaration of Helsinki, as revised in Fortaleza 2013. Written informed consent was obtained from all participants before the study, and patient anonymity and privacy has been preserved.

Sociodemographic, cognitive, and functional evaluation

A questionnaire on sociodemographic data was used to obtain information from the patients. A short Spanish version of the Questionnaire for Subjective Memory Complaints (QSMC) [19], comprised of 7 items each scored on a Likert scale from 1 to 5 (maximum 35), was administered to participants and to a family member in order to assess SCC. The QSMC items were: 1) "Do you forget where you left your things?"; 2) "Do you forget names of people you just met?"; 3) "Do you forget names of close relatives or friends?"; 4) "Do you often have a word on the tip of your tongue?"; 5) "Are you lost in familiar places where you have been before?"; 6) "Are you lost in unfamiliar places where you have been a few times?"; and 7) "Do you forget things you planned to do?".

The general cognitive functioning of participants was evaluated by the Spanish version [20] of the Mini-Mental State Examination (MMSE) [21]. Cognitive impairments in several domains were evaluated by the Spanish version [22] of the Cambridge Cognitive Assessment-Revised [22] (CAMCOG-R) [23] and other tests. We assessed: 1) attention with the Trail Making Test (A) [24] and the Attention and Calculation CAMCOG-R subscale; 2) executive functioning with Trail Making Test (B) [24], Phonological verbal fluency [25] (say in one min words starting with "p"), and the Executive Function CAMCOG-R subscale; 3) memory with by the Spanish version [26] of the California Verbal Learning Test (CVLT) [27] (which measures List A Total Recall, and Long-Delay Free Recall) and the Memory CAMCOG-R subscale; and 4) language with the Spanish version of the Boston naming test (BNT) [28], Semantic verbal fluency (animals) [25], and the Language CAMCOG-R subscale. Impairment in one cognitive domain was

considered when patients scored 1.5 SDs below age and education norms in at least two of the cognitive measures of that domain [29]. According to these criteria, 64 patients were diagnosed as multiple domain amnestic MCI, 11 as multiple-domain non-amnestic, 5 as single-domain non-amnestic, and 26 as single-amnestic (five participants were excluded because MBI diagnosis could not be confirmed from all data sources). Functional assessment was done using the Spanish version of the Lawton and Brody Index (maximum possible scoring = 8) to evaluate Instrumental Activities of Daily Living (IADL) [30].

Measurement of neuropsychiatric symptoms

To assess NPS we used: the 15-item Spanish version [31] of the Geriatric Depression Scale (GDS-15) [32], the Spanish version [33] of the Neuropsychiatric Inventory Questionnaire (NPI-Q) [34], a brief form of the NPI [35], and the Spanish version [36] of the MBI-C [13].

The MBI-C [13] includes 34 items organized in five domains: 1) decreased motivation (six items including assessments of cognitive, behavioral, and emotional apathy); 2) affective dysregulation (six questions including low mood, anhedonia, hopelessness, and guilt, and one question each for worry and panic); 3) impulse dyscontrol (12 questions describing agitation, aggression, impulsivity, recklessness, and abnormal reward and reinforcement); 4) social inappropriateness (five questions assessing sensitivity, empathy, and tact); 5) abnormal thought and perception (five questions assessing suspiciousness, grandiosity, and auditory and visual hallucinations). For each item, a "yes" or "no" question is followed by a severity rating scale of 1- mild, 2-moderate, or 3-severe. Symptoms should represent a meaningful change from baseline behaviors. A neuropsychologist administered the Spanish version of the questionnaire [37] by phone interview to a relative of the patient, to minimize travel to the health center and optimize retention. The mean time taken for the application was around 10–15 min.

Diagnosis of MBI was made via a series of semi-structured independent interviews with patients and relatives, conducted by specialized neuropsychologists, in addition to medical records, in accordance with the ISTAART-AA diagnostic criteria (Table 1). To determine criterion one, we asked for the presence of the symptoms described in the criteria over the last six months in the initial phone interview, and then confirmed them using the NPI-Q (administered to informant on the patient's assessment session). For the NPI-Q, both 1 month (proper measure of the instrument) and six-month symptom duration were queried (as required in the criteria). For criteria two and three (Table 1), information was obtained from the phone interview. Criterion four (Table 1) was obtained from the final assessment and diagnosis. Definite MBI diagnosis was made by the research team after incorporating several sources of information that included extensive clinical assessments, cognitive and neuropsychiatric testing, and this served as the reference standard for MBI-C performance validation.

Statistical analyses

Data were analyzed using SPSS v.20. Total scores were calculated for each questionnaire as well as domain scores for the MBI-C using descriptive analysis. Exploratory analyses were performed to detect any errors in the data. The prevalence of MBI diagnosis and the distribution of the MBI-C total score and domains scores in the whole sample, patients with MBI and patients without MBI were determined using frequency and descriptive analyses. Characteristics of the sample and comparisons between groups of patients with and without MBI were also performed using descriptive analysis and Independent Samples T-Tests. Furthermore, to compare one-month NPI-Q and six months NPI-Q versions in each group (with and without MBI) and in all the sample, we performed Paired Samples T-Tests. The relationships between the total score on the MBI-C and sociodemographic (age, years of education, Charlson's Comordirdity Index, and QSMC), cognitive measures (CAMCOG-R and MMSE), NPS scores (one-month NPI-Q, six-months NPI-Q, and GDS-15), and functional results (IADL) were examined using Spearman bivariate correlations because several measures did not follow a normal distribution. Binary logistic regression was used to determine the predictive value of the MBI-C, with MBI diagnosis the outcome variable and the MBI-C total score the predictor variable. To determine the utility of the MBI-C total score for diagnosing MBI and the sensitivity and specificity of the cut-off point, a ROC curve analysis was performed, with the total score on the MBI-C the contrast variable and the MBI diagnosis the state variable. The ROC curve analysis was made on a non-parametric assumption since the distribution of the scores was not normal. The level of significance was set at $p < 0.05$.

Table 2
Descriptive parameters of the sample

Variables	All ($n = 106$) Mean (SD)	Range	With MBI ($n = 15$) Mean (SD)	Range	Without MBI ($n = 91$) Mean (SD)	Range	Comparisons between groups t (106)
Age	70.04 (8.33)	50–84	71.67(6.78)	60–81	69.47 (8.6)	50–84	0.94
Years of Education	7.89 (4.07)	1–25	8.73 (4.43)	3–17	7.70 (4.03)	1–25	0.90
Charlson's Comorbidity Index	0.44 (0.67)	0–3	0.53 (0.74)	0–2	0.43 (0.67)	0–3	0.50
QSMC (patient)	16.00 (3.97)	8–29	16.33 (4.15)	8–22	16.10 (3.92)	8–29	0.21
QSMC (informant)	16.59 (4.33)	7–26	18.8 (4.16)	9–26	16.25 (4.2)	7–26	2.11*
IADL	7.20 (1.25)	5–8	6.60 (1.60)	5–8	7.29 (1.18)	5–8	–2.02
GDS-15	3.16 (2.50)	0–11	4.80 (2.42)	1–9	2.8 (2.3)	0–11	2.86**
NPI-Q 1 month	3.73 (3.25)	0–12	6.80 (2.37)	3–12	3.12 (3.09)	0–12	4.38**
NPI-Q 6 months	2.82 (3.03)	0–12	6.60 (2.13)	3–11	2.10 (2.69)	0–12	6.14**
MBI-C	5.08 (5.45)	0–23	13.93 (5.63)	7–23	3.55 (3.70)	0–12	9.22**

MBI, mild behavioral impairment; SD, standard deviation; QSMC, Questionnaire for Subjective Memory Complaints; IADL, Instrumental Activities of Daily Living; GDS-15, Geriatric Depression Scale-15 items; NPI-Q, Neuropsychiatric Inventory-Questionnaire; MBI-C, Mild Behavioral Impairment-Checklist. *significant at $p < 0.05$, **the significant at $p < 0.01$.

RESULTS

Descriptive parameters of the sample

Of the 111 participants, five were excluded because, although they were evaluated with the MBI-C, the MBI diagnosis could not be confirmed from all data sources required for the reference standard. Sixty-eight participants were women (64.2% of the sample). Descriptive parameters of the total sample and patients with and without MBI in the variables age, years of education, QSMC from the patient, Charlson's Comorbidity Index, QSMC from the informant, GDS-15, one-month and six-months NPI-Q and IADL are shown in Table 2. Descriptive parameters of cognitive measures are displayed in Table 3. Comparison between patients with and without MBI diagnosis (Independent Samples T-Tests) showed no significant differences in age, years of education, Charlson's Comorbidity Index, QSMC from the patient and Lawton and Brody Index. Significant differences were found only in QSMC from the relative, GDS-15, one-month and six-moths NPI-Q and MBI-C, with higher scores for patients with MBI (Table 2). Comparisons between patients with and without MBI diagnosis (Independent Samples T-Tests) showed no significant differences in cognitive measures (Table 3).

In each group (with and without MBI) and in the whole sample, we performed two Paired Samples T-Tests to compare the scores in the one-month NPI-Q and the six-month NPI-Q. In participants with MBI, there was no differences between one-month NPI-Q and six-months NPI-Q versions ($t = 1.38$; d.f. = 14; $p = 0.19$), whereas in participants without MBI, we found significant differences between one-month NPI-Q and six-months NPI-Q ($t = 5.06$, d.f. = 90; $p > 0.0001$), with higher scores in the one-month version. In the whole sample, we found significant differences between one-month NPI-Q and six-month NPI-Q ($t = 5.26$; d.f. = 105; $p < 0.0001$), with higher scores in the one-month version.

Descriptive parameters of the scoring in each of the five domains and total MBI-C for patients with and without MBI, as well as for all the sample, are shown in Table 4. Results from Independents Samples T-Tests showed significant differences between participants with and without MBI in four domains: decreased motivation, affective dysregulation, impulse dyscontrol, and social inappropriateness, with higher scores for participants with MBI. No significant differences were found in abnormal thought and perception (Table 4).

In the whole sample, percentile 25 was 0.0 for all domains, and 0.7 for total scoring; percentile 50 was between 0 and 1, and 3.5 for total scoring; percentile 75 and 90 were between 0 and 6 for all domains and 12 for total scoring (maximum possible for total scoring, 102) (Table 5). The total MBI-C scoring was low, 25 participants (23.6%) scored 0 and 12 participants (11.3%) scored 1 (Fig. 1). The prevalence of MBI according to ISTAART-AA diagnostic criteria was 14.2%.

For patients with MBI, percentile 25 ranged from 0 to 2 for all domains, and 9 for total scoring; percentile 50 was between 0.0 and 5, and 12 for total scoring; percentile 75 were between 0 and 8 for all domains and 19 for total scoring; percentile 90 was between 3 and 10.4 for all domains and 23 for total scoring

Table 3
Cognitive measures of the sample

Cognitive measures	All ($n = 106$)		With MBI ($n = 15$)		Without MBI ($n = 91$)		Comparisons between groups
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	t (106)
General functioning							
MMSE	26.39 (2.47)	18–30	25.4 (3.68)	18–29	26.55 (2.45)	21–30	–1.55
CAMCOG-R	82.20 (9.63)	55–102	83.07 (9.21)	68–99	82.05 (9.94)	55–102	0.37
Attention							
TMT-A (s)	75.29 (40.71)	21–202	69.67 (37.82)	31–180	77.00 (41.70)	21–202	–0.64
Attention calculation (CAMCOG-R)	6.75 (1.88)	2–9	6.8 (1.93)	3–9	6.74 (1.89)	2–9	0.01
Executive Function							
TMT-B (s)	252.08 (166.27)	NA-840	263.64 (123.35)	NA-493	251.99 (175.22)	NA-840	0.24
Phonological Verbal fluency (words that start with "p")	9.87 (5.13)	1–26	9.33 (5.03)	2–21	10.01 (5.28)	11–26	–0.46
Executive Function (CAMCOG-R)	15.83 (4.42)	6–27	16.13 (4.27)	10–25	15.86 (4.55)	6–27	0.21
Memory							
CVLT List A total recall	38.06 (12.41)	5–63	36.26 (13.76)	19–62	38.11 (12.19)	5–62	–0.53
CVLT Long Delay Free Recall	6.28 (3.93)	0–15	5.73 (5.43)	0–13	6.32 (3.69)	0–15	–0.53
Memory (CAMCOG-R)	18.23(3.69)	7–25	18.73 (3.05)	14–24	18.11 (3.86)	7–25	0.59
Language							
BNT	41.30 (9.42)	13–59	43.33 (10.36)	22–59	40.97 (9.40)	13–58	0.88
Semantic verbal Fluency (animals)	14.48 (4.44)	5–33	15.13 (4.45)	10–27	14.37 (4.50)	5–33	0.60
Language (CAMCOG-R)	24.77 (2.41)	19–30	24.93 (2.98)	19–30	24.78 (2.33)	19–29	0.22

MBI, mild behavioral impairment; SD, standard deviation; MMSE, Mini-Mental State Examination; CAMCOG-R, Cambridge Cognitive Examination-Revised; TMT-A, Trail Making Test-A form; TMT-B, Trail Making Test-B form; CVL, California Verbal Learning Test; BNT, Boston Naming Test; In TMT-B, the range is from NA, non-applicable, that means the subject was not able to complete the test, to a maximum of 840 seconds. No significant differences were found between groups in any of the cognitive measures.

Table 4
Descriptive parameters of the scores in MBI-C domains for all the sample and for patients with MBI and without MBI

MBI-C domains	All ($n = 106$)		With MBI ($n = 15$)		Without MBI ($n = 91$)		Comparisons between groups
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	F (1, 105)
Decreased motivation	1.27 (2.06)	0–11	3.93 (3.19)	0–11	0.82 (1.38)	0–6	6.37**
Affective dysregulation	1.70 (2.45)	0–11	4.60 (3.91)	0–11	1.19 (1.70)	0–7	5.67**
Impulse dyscontrol	1.92 (2.50)	0–11	4.87 (3.18)	0–11	1.41 (1.98)	0–10	5.63**
Social inappropriateness	0.15 (0.49)	0–3	0.46 (1.06)	0–3	0.09 (0.29)	0–1	2.79**
Abnormal thought and perception	0.04 (0.19)	0–1	0.07 (0.26)	0–1	0.34 (0.18)	0–1	0.59

MBI, mild behavioral impairment; MBI-C, Mild Behavioral Impairment-Checklist; SD, standard deviation. *significant at $p < 0.05$, **the significant at $p < 0.01$.

Table 5
Percentile distribution of the scores in the five domains of the MBI-C for all the sample and for patients with MBI and without MBI

MBI domains	All ($n = 106$)				With MBI ($n = 15$)				Without MBI ($n = 91$)			
	%ile 25	%ile 50	%ile 75	%ile 90	%ile 25	%ile 50	%ile 75	%ile 90	%ile 25	%ile 50	%ile 75	%ile 90
Interest, Motivation & Drive	0	0	2	4	2	3	6	9.8	0	0	1	3
Mood or Anxiety	0	1	2	5.7	1	4	8	10.4	0	0	2	4
Delay Gratification & Control	0	1	3	6	2	5	6	10.4	0	1	2	3.2
Societal Norms	0	0	0	1	0	0	0	3	0	0	0	0.2
Held Beliefs & Sensory Experiences	0	0	0	0	0	0	0	4	0	0	0	0
Total Scoring	0.7	3.5	9	12	9	12	19	23	0	2	5	10

MBI-C, Mild Behavioral Impairment-Checklist; MBI, mild behavioral impairment; %ile25, percentile 25; %ile50, percentile 50; %ile75, percentile 75; %ile90, percentile 90.

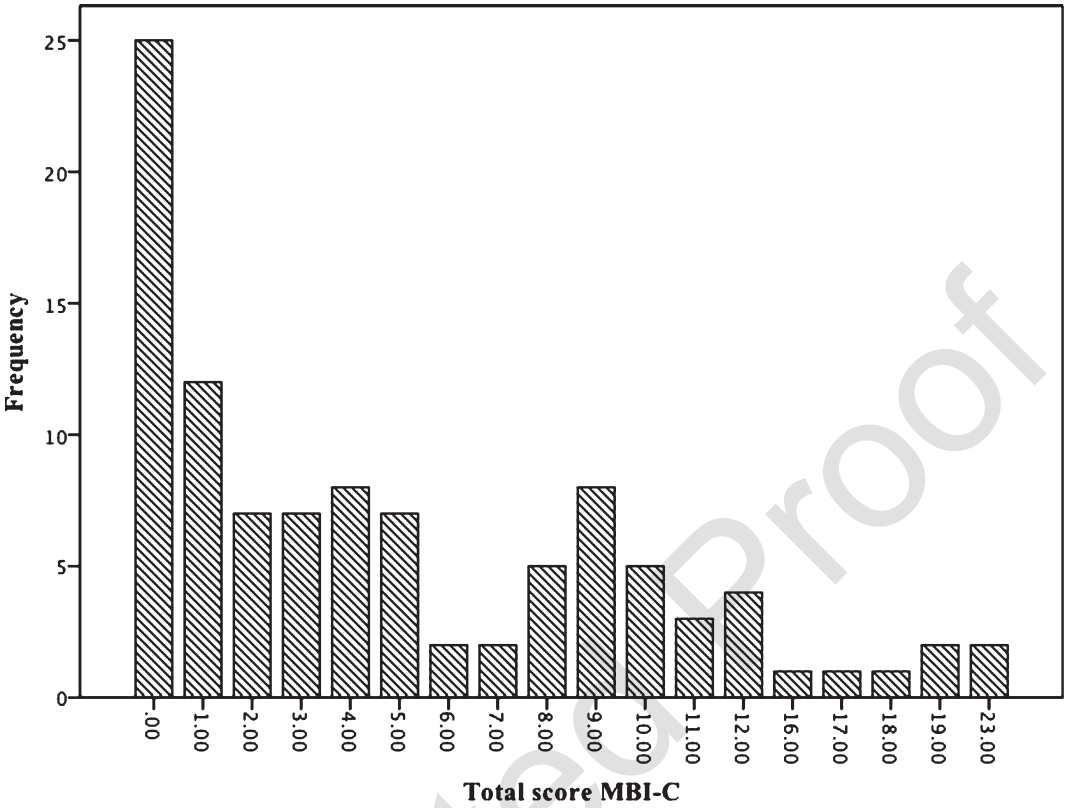

Fig. 1. Distribution of the total score in the MBI-C, determined using frequency analyses. MBI-C, Mild Behavioral Impairment-Checklist. None of the participant obtained scores between 13–15 nor 20–22.

(Table 5). For patients without MBI, percentile 25 was 0 to 2 for all domains and total scoring; percentile 50 was between 0.0 and 1, and 2 for total scoring; percentile 75 was between 0 and 2 for all domains and 5 for total scoring; percentile 90 was between 0 and 4 for all domains and 10 for total scoring (Table 5).

Spearman correlations between measures

MBI-C total scoring correlated positively with age ($\rho = 0.26$; $p < 0.01$), one-month NPI-Q ($\rho = 0.62$; $p < 0.01$), six-months NPI-Q ($\rho = 0.67$; $p < 0.01$), QSMC from the informant ($\rho = 0.46$; $p < 0.01$), GDS-15 ($\rho = 0.23$; $p < 0.05$), and negatively with IADL ($\rho = –0.26$; $p < 0.05$). No correlation was found between the MBI-C and years of education ($\rho = –0.10$; $p = 0.29$), Charlson's Comorbidity Index ($\rho = 0.07$; $p = 0.45$), QSMC from the patient ($\rho = –0.03$ $p = 0.77$), CAMCOG-R ($\rho = –0.08$ $p = 0.40$), or MMSE ($\rho = –0.14$ $p = 0.16$) (Table 6).

MBI diagnosis

Taking into account that age was positively correlated with the MBI-C total score, we tested two logistic regression models: the first one, with MBI-C total score as predictor of MBI diagnosis and the second one, adding age as covariate. The first logistic regression model showed that MBI-C score was a significant predictor of MBI diagnosis ($\beta = –0.48$; ST. E = 0.13; *Wald* = 14.22; *df* = 1, $p < 0.0001$; *OR* = 0.62 CI (95%) = 0.48–0.79). Nagelkerke R^2 showed that the model explains 64% of the variance. The Hosmer-Lemeshow test indicated a good fit for the regression model ($\chi^2 = 10.71$, *df* = 8, $p = 0.22$). The second model (with age as covariate) indicated that age was not significant ($\beta = –0.06$; ST. E = 0.06; *Wald* = 1.14; *df* = 1, $p = 0.286$; *OR* = 0.939 CI (95%) = 0.83 – 1.05), the variance explained was 64% (Nagelkerke R^2), and the goodness of fit was the same as the first one. Therefore, we decided to take the first model, with only the MBI-C total score, as the best one. ROC analysis demonstrated that MBI-C total scoring

Table 6
Spearman correlations between MBI-C total scoring and scoring in NPI-Q, CAMCOG-R, MMSE, QSMC from the patient, QSMC from the relative, GDS-15 and IADL

Neuropsychological tests	Age	Years of education	Charlson's Comorbidity Index	QSMC (patient)	QSMC (relative)	IADL	GDS-15	One month NPI-Q	Six months NPI-Q	MMSE	CAMCOG	MBI-C
Age												
Years of education	–0.41**											
Charlson's Comorbidity Index	0.19	–0.07										
QSMC (patient)	–0.85	0.09	0.04									
QSMC (relative)	0.29**	–0.07	0.13	0.32**								
IADL	–0.42**	0.13	–0.19	0.10	–0.14							
GDS-15	0.06	–0.10	–0.06	0.21*	0.17	0.09						
One-month NPI-Q	0.18	–0.10	–0.09	0.02	0.35**	–0.24*	0.38**					
Six-months NPI-Q	0.11	–0.10	–0.03	0.00	0.27**	–0.13	0.31**	0.81**				
MMSE	–0.51**	0.34**	–0.14	0.06	–0.24*	0.13	–0.03	–0.14	–0.14			
CAMCOG	–0.57**	0.58**	–0.07	–0.02	–0.24*	0.17	–0.10	–0.09	–0.06	–0.65**		
MBI-C	0.26**	–0.10	0.07	–0.03	0.46**	–0.26*	0.23*	0.62**	0.67**	–0.14	–0.08	

MMSE, Mini-Mental State Examination; CAMCOG-R, Cambridge Cognitive Examination- Revised; QSMC, Questionnaire for Subjective Memory Complaints; NPI-Q, Neuropsychiatric Inventory-Questionnaire; GDS-15, Geriatric Depression Scale-15 items; IADL, Activities of Daily Living; MBI-C, Mild Behavioral Impairment-Checklist. *significant at $p < 0.05$, **the significant at $p < 0.01$.

differentiated people with and without MBI diagnosis, and the cutoff point 6.5 reached sensitivity = 1.00, specificity = 0.78 and $AUC = 0.93$, $p < 0.001$ (Fig. 2).

DISCUSSION

To our knowledge, this is the first validation study of the MBI-C in a sample of people with MCI. We found that the prevalence of MBI in our primary care MCI sample was 14.2%, and that a cut-point of 6.5 on the MBI-C best differentiated patients with MBI from those without.

Previous studies, using traditional NPS rating scales such as the NPI-Q, indicated that the NPS prevalence in MCI populations ranges from 35% up to 85% [7, 8]. Using a transformation algorithm of the NPI score to capture criterion one of MBI, the prevalence estimated in two recent studies was 85.3% in a clinical sample [38] and 48.9% in a community sample [39]. These percentages are significantly higher than in our sample, possibly due to the short frame of reference of 1 month of symptoms, required by the NPI, compared to the more rigorous expectation of six months of symptom duration and later life onset of symptoms in the MBI-C. Thereby, the MBI-C minimizes the inclusion of transient and reactive states [11] which may cloud the diagnosis. Our results comparing the scores of the two NPI-Q versions (one and six months) show that the 6-month reference range is more rigorous. Additionally, our diagnosis was made in a stricter way by incorporating all the four ISTAART-AA criteria. Importantly, many patients from our study did not meet criterion two, because NPS were not of sufficient severity to produce at least minimal impairment in interpersonal relationships, other aspects of social functioning or ability to perform in the workplace. This requirement speaks to the clinical relevance of the ISTAART-AA MBI criteria, and may increase diagnostic specificity by excluding symptoms with no functional impact.

The findings also suggest that the phone administration of the MBI-C is useful for detecting MBI in people with MCI. The cutoff point of 6.5 significantly classified people with MBI diagnoses with a sensitivity of 100% and a specificity of 78.20%. Since the MBI-C was developed specifically as a case ascertainment instrument for the ISTAART-AA MBI criteria, and structured to be consistent with the MBI domains, high sensitivity and specificity was expected. The telephone administration could be highly beneficial in populations that are dispersed, where the residents have difficulties traveling to the health care centers, or when the informants are not able to go there due to health reasons or agenda. Even for participants and clinic patients who live close to research or clinical centers, collateral data gathered via telephone MBI-C administration can generate important information on the natural history and type of NPS in participants, coloring and refining dementia risk assessment. Moreover, in our study, a clinician conducted the MBI-C by phone, but more investigations should be done with face-to-face assessments to generate other validations and to test the equivalence of the telephone and the face-to-face presentations.

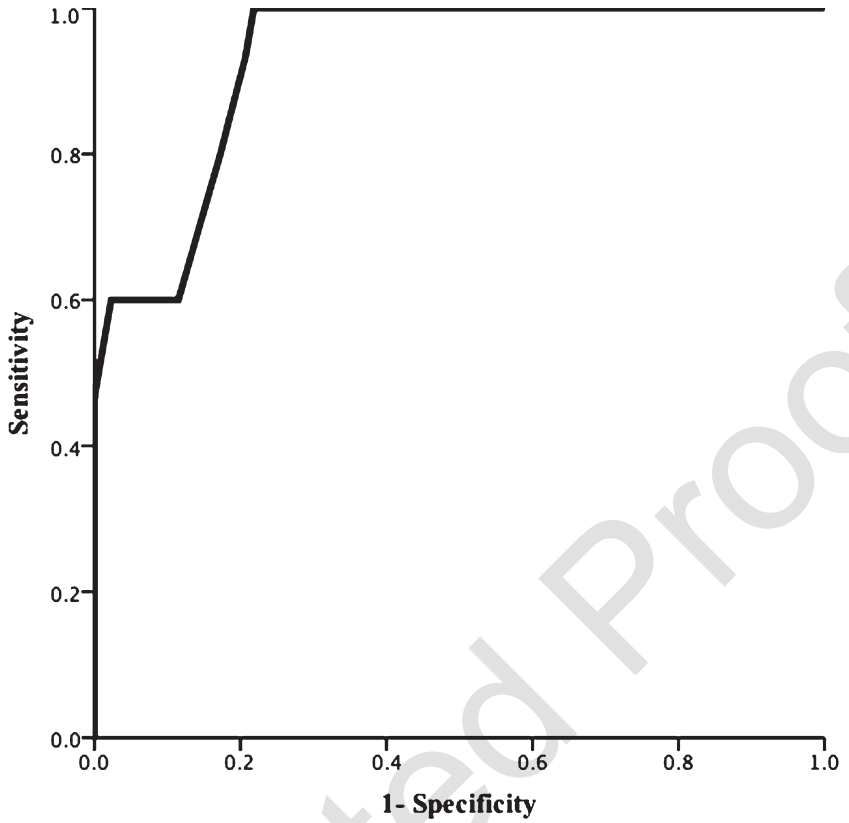

Fig. 2. ROC curve, with the total score on the MBI-C as the contrast variable and the MBI diagnosis as the state variable. MBI-C, Mild Behavioral Impairment-Checklist; MBI, mild behavioral impairment.

The MBI-C total score showed a mean significant positive correlation with one-month NPI-Q, six-month NPI-Q, and with GDS-15, indicating the validity of the MBI-C to assess NPS. In accordance with these results, our analyses have also shown that patients with MBI have significantly higher scores on the NPI-Q, GDS-15, and in four of the five domains of the MBI-C (decreased motivation, affective dysregulation, impulse dyscontrol, and social inappropriateness), than patients without MBI. NPS are common in the early clinical stages of neurocognitive disorders, with prevalence estimates ranging from 35–85%, due to differences in study setting, demographics, MCI diagnosis, and instruments used [7, 8]. Depression is one of the most common symptoms in MCI, with a recent meta-analysis estimating prevalence at 32%, but being higher in clinical than in community samples [40]. MBI-C correlation with the GDS provides reassurance that depressive symptoms are captured with the MBI-C.

The MBI-C detected subtle NPS that were correlated with functional impairment as measured by the Lawton and Brody IADL Index. This finding suggests that the emergence of NPS may be related to an early functional impairment. This result is in accordance with criterion two of the MBI diagnosis [11], which stipulates that NPS produce minimal impairment in interpersonal relationships, other aspects of social functioning, or ability to perform at the workplace. Commonly, people with MCI have problems performing complex functional tasks which they used to perform in the past [18]. In MBI, these impairments in social, occupational, or interpersonal function must be related to changes in personality and behavior, and not due to changes in cognition [11]. This result highlights the importance of an early assessment of functionality in people at risk of cognitive impairment. While the expectation that functional impairment is due to NPS, and that this increases diagnostic specificity, the converse argument also applies. It is possible that awaiting functional impairment may result in diagnostic delays, missing the mildest or earliest of symptoms, and chances for early intervention and clinical trial enrollment [41].

Our results have also indicated that patients with MBI have higher scores on QSMC from the informants than those without MBI. The significant positive correlation between MBI-C and subjective cognitive performance as measured by the QSMC is relevant, taking into account that SCC are an important criterion for the diagnosis of MCI [18]. These findings highlight the importance of testing NPS in people with MCI because they may be early markers of cognitive impairment and therefore early indicators of dementia. No correlation was found between the MBI-C and QSMC from the patient. Juncos-Rabadán et al. [42] concluded that memory difficulties reported by the informant, not the participants themselves, have a greater prognostic value predicting objective performance. Further studies are needed to determine the relationship between SCC and NPS, and which type of SCC (reported by the patients themselves or by the informants) are more accurate. No correlation was found between the MBI-C and objective cognitive measures (CAMCOG-R and MMSE). This supports the notion that while MBI and MCI can co-occur, they reflect different pre-dementia syndromes (neurobehavioral and neurocognitive), and that MBI is not simply a function of cognitive impairment [11]. Future investigations on this interesting topic are recommended.

Our study is characterized by several strengths. A detailed neurocognitive assessment, including tasks with norms for age and education, was performed. To assess cognitive deficits, not only the MMSE, a screening test, but also the CAMCOG-R, an extensive battery, was conducted. Hence, classification of participants was made by diagnostic criteria, instead of cutoff points in screening tasks. Further, we used the MBI-C, an instrument specially designed to detect NPS in pre-dementia populations and the all four MBI ISTAART criteria. Notwithstanding the strengths, there are also some limitations. Our study provides prevalence estimates for MBI in those with MCI, but not in those with SCC or dementia. While the cross-sectional design has provided validation of the MBI-C for measuring MBI in MCI patients, it is not possible to make any conclusions in relation to changes in prevalence over time, nor risk factors for evolution to dementia. Longitudinal data is needed to determine the prognostic utility of the MBI-C.

All the results together suggest that the Spanish version of the MBI-C is especially useful for detecting MBI in people with MCI. There are several implications of this finding. First, the MBI construct is in keeping with the inclusion of behavioral symptoms in the 2011 National Institute on Aging–Alzheimer's Association (NIA-AA) consensus recommendations for diagnosis of all-cause dementia [15]. The basis of these criteria is the assumption that neurodegeneration may manifest with changes in personality, behavior, or psychiatric symptoms, prior to cognitive impairment, depending on the type, location, and impact of the underlying pathology. Literature has suggested, however, that poor recruitment and retention in the early phase illness has contributed to the lack of success in dementia disease modifying clinical trials [41]. Historically, older adults with later onset NPS, who did not show obvious cognitive impairment would receive a psychiatric diagnosis, and the possibility of neurodegenerative disease was often overlooked [43, 44], resulting in inappropriate, delayed, or suboptimal care [45]. MBI distinguishes between formal psychiatric illness/chronic psychiatric symptomatology versus new onset psychiatric symptoms in older adults, the latter of which are core to the MBI construct of the at-risk state. The MBI-C may be beneficial in case detection for observational and intervention studies, selecting an enriched sample for biomarker screening and clinical trial enrollment, disentangling the confusion sometimes created by later life NPS [13]. As it is freely available in multiple translations (available at http://www.MBItest.org), the MBI-C is a simple, efficient, and scalable instrument that could be used in clinical settings, research environments, or broader public health and screening initiatives. Second, while our study is focused on the MBI-C total score, differences in prediction of cognitive impairment based on the various aggregate domain scores need to be determined. In the ISTAART-AA MBI criteria, symptoms are divided into the following domains: decreased motivation [46, 47], affective dysregulation [48, 49], impulse dyscontrol [4, 50], social inappropriateness [51, 52], and abnormal though or perception [53, 54]. Just as different NPS may be associated with different types of dementias, different MBI domains may predict different MCI and dementia subtypes, which may have implications for treatment [13]. The MBI research agenda, as expressed by the ISTAART NPS professional interest area, describes the next steps for investigation [55]. Future studies should determine the predictive value of MBI, with and without MCI, for incident cognitive decline and dementia in a variety of cohorts. Additionally, biomarker correlates of MBI are required, including imaging, known dementia proteinopathies, as well as novel markers. The

overall goal is to better describe and capture early manifestations of neurodegenerative disease in order to intervene earlier. MBI-C validations are early steps in this research agenda, but represent foundational elements, on which to build subsequent knowledge.

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