Review Article

A Systematic Review of Neuropsychiatric Symptoms in Mild Cognitive Impairment

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Abstract. Mild cognitive impairment (MCI) is a clinical concept proposed as an intermediate state between normal aging and dementia. This condition has multiple heterogeneous sources, including clinical presentation, etiology, and prognosis. Recently, the prevalence and associated features of neuropsychiatric symptoms (NPS) in MCI have been described. We systematically searched the PubMed database (last accessed on August 31, 2008) for articles on NPS in MCI. Included articles used strict selection criteria, and outcome variables were extracted in duplicate; of the 27 articles included, 14 (52%) used prospective cohorts. The global prevalence of NPS in MCI ranged from 35% to 85%. The most common behavioral symptoms were depression, anxiety, and irritability. Hospital-based samples reported a higher global prevalence of NPS than population-based studies; this discrepancy probably reflected differences in demographics, study setting, MCI diagnostic criteria, and behavioral instruments used. Prospective studies showed that NPS, particularly depression, may represent risk factors for MCI or predictors for the conversion of MCI to Alzheimer's disease (AD). NPS are very prevalent in subjects with MCI, displaying a similar pattern of symptoms compared to dementia and AD. Large cohort studies using standardized MCI criteria and behavioral instruments are required to evaluate the prognostic role of NPS in MCI.

Keywords: Alzheimer's disease, behavior, dementia, depression, incidence, mild cognitive impairment, neuropsychiatric symptoms, predictors, prevalence, risk factors

INTRODUCTION

The clinical concept of mild cognitive impairment (MCI) identifies subjects who are in an intermediate state between normal aging and dementia [1–4]. MCI is currently defined as a syndrome characterized by an impairment of memory or other cognitive functions, which does not have an effect on or slightly impairs an individual's instrumental functional abilities, in subjects who have not been clinically diagnosed with dementia [4]. MCI appears to be an extremely heterogeneous condition in terms of etiology, clinical presentation, and outcome [1,5]. The syndrome can be divided into two broad subtypes: an amnestic type (aMCI), characterized by reduced memory functioning, and a non-amnestic type (naMCI) in which cognitive functions other than memory are impaired [3].

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While aMCI seems to represent an early stage of Alzheimer's disease (AD), the outcomes of naMCI appear to be more heterogeneous, and they include an evolution toward vascular dementia, frontotemporal dementia, and dementia with Lewy bodies [3]. However, MCI is a syndrome of increased risk but not a prodromal phase for impending dementia. Indeed, a significant rate of reversion from MCI to normal cognition and functioning has been observed [6,7], thus suggesting that an underlying, potential, reversible cause of MCI could also be neuropsychiatric comorbidity, with an inherent implication for treatment [8,9].

As is the case with dementia, neuropsychiatric symptoms (NPS) have not been included in the concept of MCI and only recently have various studies described the neuropsychiatric features of the condition [10]. NPS, which occurs in at least one-third of MCI subjects [10], have been associated with worse cognitive performance, functional disability, and mild extrapyramidal signs [11–14]. Furthermore, they have been proposed as independent risk factors for the development of MCI [15–18] as well as predictors of conversion from MCI to dementia and AD [18–24]. However, the prognostic role of NPS in MCI is still under debate. In this systematic review, we summarize the current evidence on NPS in MCI.

METHODS

Search strategy

All studies which included an assessment of NPS in subjects with MCI were eligible for inclusion (see below for details of criteria used). In order to identify the articles, we systematically searched the PubMed, National Library of Medicine database for English-language articles (last accessed on August 31, 2008, and including Epub reports). Furthermore, we found additional papers by performing a manual search of the reference lists of relevant retrieved articles, the tables of contents of relevant journals, and one previous systematic review published on NPS in MCI [10].

We combined the results of searches in PubMed into 2 separate domains: 1) *mild cognitive impairment* [keyword]; and 2) *delusions, hallucination, psychomotor agitation, aggression, depression, anxiety, euphoria, irritable mood* [MeSH Terms] or *neuropsychiatric, behavioral and psychological symptoms, psychosis, delusion, hallucination, agitation, aggression, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior and wandering* [keywords].

Data extraction

A total of 461 articles were identified through database searches. Studies were subsequently selected for inclusion in our systematic review if they met all of the following criteria: 1) the study had to include an MCI definition, which was not only based on Mini-Mental State Examination [25] averages and/or other global cognitive or clinical scales (e.g., Clinical Dementia Rating scale – CDR) [26], but the definition necessitated broader criteria, including specific cognitive testing; 2) NPS had to be collected using standardized instruments, excluding NPS obtained from subjective reports; 3) regarding the descriptive epidemiological features of NPS in MCI, the prevalence and/or incidence rates of NPS had to be described in the text. With regard to the associated factors of NPS in MCI, the risk factors for MCI development or the conversion from MCI to dementia, chi-square analysis, odds ratios, relative risks or other measures of association had to have been reported; and 4) the study had to include a minimum MCI sample of 40.

The search was run in two phases. Firstly, the titles and abstracts were read by two authors (C.C. and S.E.) and, if we were uncertain about data from the title and the abstract, the full study was obtained. A total of 429 articles were excluded, based on reviewing titles and abstracts, thus leaving 32 reports for full review. These totaled 39 papers because an additional seven articles were identified in the manual search of references. Secondly, data were extracted independently by two investigators (R.M. and F.M.), using a structured proforma, including the following information: study type (cross-sectional or longitudinal); study setting (hospital-based, GP-based, clinical trial, clinico-pathological study, population-based); number of MCI subjects included at baseline; length of follow-up in years; mean age of MCI samples; percentage of females within the MCI groups; behavioral instruments used to evaluate NPS; the MCI diagnostic criteria adopted and subtypes included; excluded groups; and main findings. The latter included the prevalence rates of NPS in MCI and the associated factors for each NPS in MCI in cross-sectional studies. Furthermore, the incidence rates of NPS in MCI and the role of each NPS as a putative risk factor for MCI or as predictors for the evolution from MCI to dementia and AD in cohort studies were examined. Original methodological articles belonging to prospective cohort studies, describing study characteristics for MCI criteria and NPS assessment, were evaluated if needed. Duplicate papers were also
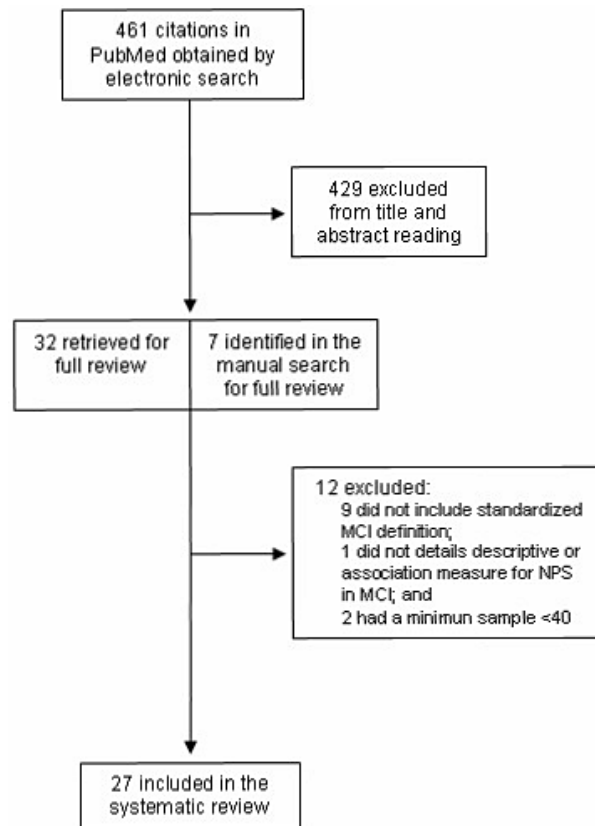
Fig. 1. Flow diagram of search strategy and study selection.

sought. Disagreements were discussed and if consensus was not reached, a third author (R.C.) was the final arbitrator. Specifically, 33 out of 39 reviewed articles were similarly judged by the two reviewers and the inclusion of the remaining six papers was definitively resolved by the final arbitrator. Using Cohen's kappa coefficient (a statistical measure of inter-rater agreement for categorical data), the reliability in our selection process between the two reviewers was "almost perfect" (kappa = 0.85), according to the Landis and Kock interpretation of kappa values [27]. Overall, from 39 articles that were reviewed, only 27 were eligible for inclusion (see Fig. 1). Two out of the six papers judged by the final arbitrator were finally included in the full review process, including 27 articles, while 4 were excluded.

Study design, sample size, demographics and outcomes

The study characteristics are detailed in Table 1. Briefly, of a total of 27 selected articles: 12 were hospital-based studies (7 cross-sectional and 5 longitudinal) [13,14,16,20–22,24,28–32]; 2 were multicenter cross-sectional general practitioners studies [33,34]; 1 was from a large multicenter clinical trial [12]; 1 was a clinicopathological study of older Catholic clergy performed throughout the USA [35]; and there were 11 population-based studies (3 cross-sectional, 7 longitudinal and 1 which reported both cross-sectional and longitudinal data) [11,15,17–19,23,36–40].

The sample size for studies evaluating NPS in MCI varied enormously within studies, ranging from 44 to 2,879 subjects at baseline; the median sample size was, however, equal to 121 subjects. For longitudinal studies, the length of follow-up was similar, ranging from a mean of 2.0 to 5.8 years. Mean age at baseline varied within studies ranging from 65.2 to 80.6 years. Similarly, the percentage of females included differed within studies, ranging from 35% to 75%.

Of the 27 articles included in the systematic review concerning outcomes, 9 described the descriptive epidemiological features of NPS in MCI (e.g., prevalence and incidence rates) [12,29–34,36,40], while 14 re-

Table 1
Neuropsychiatric symptoms in mild cognitive impairment: study characteristics (according to study setting)

Source [study reference]	Study design	Study setting	No. of MCI (baseline)	Follow-up (years)	Age baseline (years)	Sex (female)	Behavioral instrument	Findings
Bruce, 2008 [28]	cross-sectional	hospital-based (memory clinic)	82	–	74.5	NS	BDI 21-item	fewer depressive symptoms are associated with poorer memory functioning
Gabryelewicz, 2004 [29]	cross-sectional	hospital-based (memory clinic)	102	–	70	71%	MADRS, DSM-IV	prevalence of depression
Gabryelewicz, 2007 [20]	longitudinal	hospital-based (memory clinic)	105	3.0	69.3	68%	MADRS, DSM-IV	depression predicts conversion from MCI to dementia
Geda, 2004 [30]	cross-sectional	hospital-based (division of primary care medicine)	54	–	79	54%	NPI	prevalence of NPS
Geda, 2006 [16]	longitudinal	hospital-based (division of primary care medicine)	none (50 at follow-up)	3.5	NS	NS	GDS 15-item	depression risk factor for MCI development
Houde, 2008 [21]	longitudinal	hospital-based (memory clinic)	60	4.3	74.5	NS	GDS 30-item	depression predicts conversion from MCI to AD
Hudon, 2008 [13]	cross-sectional	hospital-based (memory clinic)	44	–	65.2	57%	GDS 5-item	depression is associated with worse cognitive performance
Lopez, 2005 [31]	cross-sectional	hospital-based (memory clinic)	228	–	70.1	51%	CERAD-BRSD, DSM-IV	prevalence of NPS
Modrego and Ferrandez, 2004 [22]	longitudinal	hospital-based (memory clinic)	114	3.0	72.8	63%	GDS 30-item, DSM-IV	depression predicts conversion from MCI to AD
Rozzini, 2008a [32]	cross-sectional	hospital-based (memory clinic)	120	–	70.3	62%	NPI	prevalence of NPS
Rozzini, 2008b [14]	cross-sectional	hospital-based (memory clinic)	150	–	71.7	64%	NPI	NPS are associated with motor symptoms in MCI
Teng, 2007 [24]	longitudinal	hospital-based (memory clinic)	51	2.0	73.9	35%	NPI	NPS are a predictor for MCI progression to AD
Luck, 2007 [33]	cross-sectional	multicenter attending general practitioners	425	–	NS	NS	GDS 15-item	prevalence of depressive symptoms
Weyerer, 2003 [34]	cross-sectional	multicenter attending general practitioners	817	–	NS	NS	GDS 15-item	prevalence of depression
Feldman, 2004 [12]	cross-sectional	multicenter clinical trial	1,010	–	70.4	52%	NPI	prevalence of NPS

Table 1, continued

Source [study reference]	Study design	Study setting	No. of MCI (baseline)	Follow-up (years)	Age baseline (years)	Sex (female)	Behavioral instrument	Findings
Wilson, 2008 [35]	longitudinal	clinicopathological study of older Catholic clergy	none (319 at follow-up)	3.2	NS	NS	CES-D 10-item	no evidence of an increase of depressive symptoms in the prodromal phase of AD
Artero, 2008 [19]	cross-sectional and longitudinal	multicenter population-based	2,879	4.0	74.6	65%	CES-D 20-item MINI module for major depressive episode	– prevalence of depression – depression risk factor for MCI progression to dementia
Barnes, 2006 [15]	longitudinal	multicenter population-based	none (296 at follow-up)	6.0	NS	NS	CES-D 10-item	depressive symptoms risk factor for MCI development
Chan, 2003 [11]	cross-sectional	population-based	121	–	78.4	75%	NPI depression subscale, BSRS	– prevalence of NPS – associated factors for MCI
Lopez, 2003 [17]	longitudinal	multicenter population-based	577	5.8	75.4	59%	CES-D 10-item	depression risk factor for MCI development
Lyketsos, 2002 [36]	cross-sectional	multicenter population-based	320	–	75	60%	NPI	prevalence of NPS
Muangpaisan, 2008 [37]	cross-sectional	population-based	77	–	66.3	NS	NPI	– prevalence of NPS – associated factors for MCI
Palmer, 2007 [23]	longitudinal	population-based	47	3.0	NS	NS	CPRS	– prevalence of depressive and anxiety symptoms – anxiety symptoms are a predictor of MCI conversion to AD
Panza, 2008a [38]	longitudinal	multicenter population-based	139	3.5	80.6	48%	GDS 30-item	depressive symptoms are not risk factors for MCI development
Panza, 2008b [39]	longitudinal	multicenter population-based	139	3.5	80.6	48%	GDS 30-item	depressive symptoms are not associated with conversion from MCI to AD
Solfrizzi, 2007 [40]	longitudinal	multicenter population-based	139	3.5	80.6	48%	GDS 30-item	prevalence and incidence of depressive symptoms
Stepaniuk, 2008 [18]	longitudinal	multicenter population-based	240 (baseline) 115 (1st follow-up) 44 (2nd follow-up)	2 follow-ups of 5-year each	NS	NS	CAMDEX, section H	– NPS are a predictor for MCI development – NPS a predictor for MCI progression to dementia

Abbreviations: MCI, Mild Cognitive Impairment; NS, not specified; BDI, Beck Depression Inventory; MADRS, Montgomery-Asberg Depression Rating Scale; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; NPI, Neuropsychiatric Inventory; NPS, neuropsychiatric symptoms; GDS, Geriatric Depression Scale; AD, Alzheimer's disease; CERAD-BRSD, Consortium to Establish a Registry for Alzheimer's Disease Behavioral Rating Scale for Dementia; CES-D, Center for Epidemiological Studies Depression Scale; MINI, Mini International Neuropsychiatric Interview; BSRS, Behavioral Symptom Rating Scale; CPRS, Comprehensive Psychopathological Rating Scale; CAMDEX, Cambridge Examination for Mental Disorders of the Elderly.

ported the analytic epidemiological features of NPS in MCI (e.g., associated factors for NPS in MCI, NPS as risk factors for MCI development or as predictors for MCI conversion to dementia) [13–18,20–22,24,28,35, 38,39]. Furthermore, the remaining 4 articles reported both the descriptive and analytical epidemiological features of NPS in MCI [11,19,23,37].

Diagnostic criteria for MCI, included subtypes and excluded groups

Included studies adopted different sets of diagnostic criteria for MCI (Table 2). Briefly, 4 studies [16, 22,30,37] used the original clinical criteria for aMCI proposed by Petersen et al. [2], where a diagnosis of MCI is made if the subjects met the following criteria: 1) memory complaint (preferably corroborated by a caregiver); 2) normal activities of daily living; 3) normal general cognitive function; 4) abnormal memory on cognitive testing (generally performance ⩾ 1.5 SD below age and education-adjusted scores); and 5) the absence of dementia (clinical judgment). Two additional studies [20,29] used Petersen's criteria but also included subjects with some minor impairment in the non-memory domains in the aMCI group.

Nine studies [13–15,17,24,28,31,32,36] relied on MCI modified criteria of Winblad and colleagues [4] which includes: 1) evidence of cognitive decline, measured either by self and/or caregiver report, in conjunction with deficits on objective cognitive tasks, and/or evidence of decline over time on objective neuropsychological tests (generally performance ⩾ 1.5 below age and education-adjusted scores); 2) preserved basic activities of daily living/minimal impairment in complex instrumental functions; and 3) the absence of dementia (clinical judgment). Four additional studies used Winblad's criteria, adopting a different cutoff point for rating cognitive decline (performance ⩾ 1.0 SD below or in the lower quartile range for age and education-adjusted scores) [19,21,33,34]. One of these four studies did not adopt the criteria of subjective cognitive complaints [34].

Six population-based studies mainly used a neuropsychological-driven approach to define MCI subjects with the adoption of different age- and education-adjusted cut-off points after excluding dementia cases [18,23,35,38–40]. Data from the clinical trial used a combination of the New York University delayed paragraph recall test and a CDR score of 0.5 [12]. Finally, in one article, MCI was only classified by relying on neuropsychological performance [11].

MCI has two main subtypes: aMCI, which is primarily characterized by impaired memory with relatively unimpaired or less-impaired functioning in other cognitive domains; and naMCI, characterized by impairment in one or more cognitive domains other than memory, including language, attention, executive functioning, etc. [3].

In brief, of the 27 selected articles included in this review, there were 7 hospital-based studies which focused on aMCI [13,16,20–22,29,30] while 5 described both aMCI and naMCI subjects [14,24,28,31,32]. In the two multicenter cross-sectional GP studies [33,34], the authors described data from aMCI in addition to naMCI, while the multicenter clinical trial included only aMCI subjects [12]. The clinicopathological study of older Catholic clergy included a sample of MCI without detailing the type of cognitive impairment [35]. Regarding population-based studies, 4 articles included aMCI subjects [37–40], 1 was both aMCI and naMCI [23], and 6 described the entire MCI group [11,15, 17–19,36]. Five out of these 6 included both aMCI and naMCI [11,15,17,19,36] while one gave no details of the type of cognitive impairment [18].

With reference to the excluded groups, the presence of major depression was an exclusion criterion in 5 studies [12,13,20,29,37], and, in one of these, other psychiatric disorders and those subjects receiving psychotropic drugs in amounts affecting cognition were also excluded [37]. In the international multicenter Investigation in the Delay to Diagnosis of AD with Exelon (InDDEX) trial [12], subjects with no, very mild, or major depression were also excluded. Lastly, in the studies by Geda and colleagues [16,30], subjects with severe neurologic and psychiatric conditions interfering with cognitive assessment and persons receiving psychotropic drugs in amounts affecting cognition were excluded.

Behavioral instruments used

Studies included in this review have adopted several different behavioral instruments for the evaluation of NPS (Table 1), a brief description of which is outlined in Table 3. Twelve studies out of 27 included in this review used standardized instruments, assessing depressive symptoms [13,15–17,21,28,33–35,38–40]; in 4 other cases information from depression scales were corroborated using *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV) [41] criteria for major depression [19,20,22,29]. All adopted depressive scales were developed or applicable to elder-

Table 2

Neuropsychiatric symptoms in mild cognitive impairment: diagnostic criteria adopted, included subtypes, and excluded groups

Source [study reference]	MCI criteria			MCI subtypes			Excluded groups
	Subjective cognitive complaints	*IADL impairment (slight)*	*Definition of cognitive impairment*	*MCI (all)*	*aMCI*	*naMCI*	
Bruce, 2008 [28]	Yes	Yes	[a]Winblad's modified MCI criteria [4]	+	+	+	
Gabryelewicz, 2004 [29]	Yes	No	[b]Petersen's original MCI criteria [2], but with impairment in non-memory domain		+°		subjects with severe DSM-IV major depression
Gabryelewicz, 2007 [20]	Yes	No	Petersen's original MCI criteria [2], but with impairment in non-memory domain		+°		subjects with severe DSM-IV major depression
Geda, 2004 [30]	Yes	No	Petersen's original MCI criteria [2]		+		persons with severe neurologic and psychiatric conditions interfering with cognitive assessment and persons receiving psychotropic drugs in amount affecting cognition
Geda, 2006 [16]	Yes	No	Petersen's original MCI criteria [2]		+		persons with severe neurologic and psychiatric conditions interfering with cognitive assessment and persons receiving psychotropic drugs in amount affecting cognition
Houde, 2008 [21]	Yes	Yes	Winblad's modified MCI criteria [4] (⩾1.0 SD below AEAS on standard memory tests)		+°		
Hudon, 2008 [13]	Yes	Yes	Winblad's modified MCI criteria [4]		+°		subjects with DSM-IV major depression
Lopez, 2005 [31]	NS	Yes	Winblad's modified MCI criteria [4]		+	+	
Modrego and Ferrandez, 2004 [22]	Yes	No	Petersen's original MCI criteria [4]		+		
Rozzini, 2008a [32] and Rozzini, 2008b [14]	Yes	Yes	Winblad's modified MCI criteria [4]		+	+	
Teng, 2007 [24]	Yes	Yes	Winblad's modified MCI criteria [4]		+	+	
Luck, 2007 [33]	Yes/No	Yes	Winblad's modified MCI criteria [4] (⩾1.0 SD below AEAS on standard cognitive tests)		+	+	
Weyerer, 2003 [34]	No	Yes	Winblad's modified MCI criteria [4] (⩾1.0 SD below AEAS on standard cognitive tests)		+°	+	
Feldman, 2004 [12]	No	Yes	impaired performance on NYU delayed paragraph recall, no dementia and CDR = 0.5		+		subjects with no o very mild depression as well as DSM-IV major depression

Table 2, continued

Source	MCI criteria			MCI subtypes			Excluded groups
[study reference]	*Subjective cognitive complaints*	*IADL impairment (slight)*	*Definition of cognitive impairment*	*MCI (all)*	*aMCI*	*naMCI*	
Wilson, 2008 [35]	NS	NS	identified by the neuropsychologist after the examining physician excluded dementia	+			
Artero, 2008 [19]	Yes	Yes	Winblad's modified MCI criteria [4] (cognitive performance in the lower quartile range for AEAS on standard cognitive tests)	+∗			
Barnes, 2006 [15]	Yes/no	Yes	Winblad's modified MCI criteria [4]	+∗			
Chan, 2003 [11]	No	No	⩾ 1.5 SD on one test or ⩾ 1 SD on two or more tests below AEAS on standard cognitive tests	+∗			
Lopez, 2003 [17]	Yes/No	Yes	Winblad's modified MCI criteria [4]	+∗			
Lyketsos, 2002 [36]	Yes/No	Yes	Winblad's modified MCI criteria [4]	+∗			
Muangpaisan, 2008 [37]	Yes	No	Petersen's original MCI criteria [2]		+		persons with DSM-IV major depression or other psychiatric disorders and those receiving psychotropic drugs in amount affecting cognition
Palmer, 2007 [23]	Yes	No	⩾ 1.0 SD below AEAS on standard cognitive tests and no dementia	+	+	+	
Panza, 2008a [38] Panza, 2008b [39] and Solfrizzi, 2007 [40]	No	Yes	impaired memory performance (⩽ 10th percentile of the distribution of AEAS after exclusion of prevalent dementia cases at entry)	+			
Stepaniuk, 2008 [18]	Yes	NS	physicians and neuropsychologists independently diagnosed the subjects after excluding dementia; confirmed by a consensus conference	+			

Abbreviations: MCI, Mild Cognitive Impairment; IADL, Instrumental Activities of Daily Living; aMCI, amnestic MCI; naMCI, non-amnestic MCI; +, MCI group included; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; SD, standard deviation; AEAS, age- and education-adjusted scores; NS, not specified; NYU, New York University; CDR, Clinical Dementia Rating scale.
[a]Includes: (1) cognitive decline (self and/or informant report and impairment on objective cognitive tasks and/or evidence of decline over time on objective cognitive tasks), (2) preserved basic activities of daily living/minimal impairment in complex instrumental functions, (3) no dementia (clinical judgement).
[b]Includes: (1) memory complaint, (2) normal activities of daily living, (3) normal general cognitive function, (4) abnormal memory for age, and (5) no dementia (clinical judgement).
For [a] and [b], excluded were specified in the table, cognitive impairment generally implies performance ⩾ 1.5 SD below AEAS on standard cognitive tests.
*These groups include both aMCI and naMCI subjects. °Together with aMCI subjects, these groups also included multi-domain aMCI individuals.

Table 3
Neuropsychiatric symptoms in mild cognitive impairment: behavioral instruments used

Use/ Instrument [reference]	Rating	Time taken (min)
Depression		
BDI [43]	self-rated	20
MADRS [44]	by trained interviewer with subject	20
GDS [45]	self-administered	5–10
CES-D [42]	self-administered	5
Behavioral and psychological symptoms in demented subjects		
NPI (10 behavioral symptoms: delusions, hallucinations, dysphoria, anxiety, agitation, euphoria, disinhibition, irritability, apathy, aberrant motor behavior) [47]	by clinician in interview with caregiver	10
BSRS (12 items assessing the following behavioral symptoms: social interaction, hallucinations, delusions, wandering, hoarding, yelling or cursing, sleep problems, emotional instability, problem urination, resisting help with everyday activities, verbal perseveration and physical aggression) [48]	by trained interviewer with caregiver	10–15
CERAD-BRSD (46 items assessing the following behavioral symptoms: depressive features, psychotic features, defective self-regulation, irritability/agitation, vegetative features, apathy, aggression and affective lability) [49]	by trained interviewer with subject	20–30
Global measures of psychiatric symptomatology		
MINI (a short structured diagnostic interview for the evaluation of DSM-IV and ICD-10 psychiatric disorders, including mood disorders, anxiety disorders, somatoform disorders, psychotic disorders, etc.) [52]	by trained interviewer with subject	15
CPRS (65 items covering a broad range of functional psychopathology in psychotic, mood and neurotic disorders as well as somatic anxiety symptoms) [50]	by trained interviewer with subject	50
*CAMDEX section H (collected information, enables a psychiatric diagnosis to be made: dementia, delirium depression, anxiety or phobic disorder, paranoid or paraphrenic illness and other psychiatric disorder) [51]	by trained interviewer with carer	20

Abbreviations: BDI, Beck Depression Inventory; MADRS, Montgomery-Asberg Depression Rating Scale; GDS, Geriatric Depression Scale; CES-D, Center for Epidemiological Studies Depression Scale; NPI, Neuropsychiatric Inventory; BSRS, Behavioral Symptom Rating Scale; CERAD-BRSD, Consortium to Establish a Registry for Alzheimer's Disease Behavioral Rating Scale for Dementia; MINI, Mini International Neuropsychiatric Interview; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; ICD-10, International Classification of Diseases, 10th edition; CPRS, Comprehensive Psychopathological Rating Scale; CAMDEX, Cambridge Examination for Mental Disorders of the Elderly. *This instrument is not a *pure* behavioral scale but it is a standardized interview for the diagnosis of mental disorders in the elderly with special reference to dementia.

ly subjects [42–46]. The remaining 11 studies adopted behavioral instruments, evaluating a broad variety of NPS [11,12,14,18,23,24,30–32,36,37].

Some of these multidimensional instruments were specifically developed for elderly subjects with cognitive impairment [47–49], while others represented global measures of psychiatric symptomatology [50–52]. Of the comprehensive scales, the most commonly used (7 studies) was the Neuropsychiatric Inventory (NPI) [47]. Overall, the majority of behavioral instruments used were to be administered to the patient or his/her caregiver or both [44,47–52] while others were self-administered [42,43,45].

RESULTS

1. Prevalence of NPS in MCI

An analysis of selected articles has revealed that NPS constitute very common clinical features in subjects with MCI. Indeed, considering at least one NPS, data from some of these studies produced prevalence rates ranging from 35% to 85% in MCI patients (Table 4) [11, 12,30,32,36]. Similar to that previously described for dementia and AD [53,54], the 5 studies investigating the prevalence of NPS in MCI via the NPI demonstrated that three symptoms (depression, anxiety, and irritability) consistently comprise the most common be-

Table 4
Neuropsychiatric symptoms in mild cognitive impairment: prevalence rates reported
by the included studies

Symptom	Study setting	Prevalence, %	Behavioral instrument [study reference]
Any NPI symptom	*Hospital-based*	35–85	NPI [30,32]
	GPs	NA	
	Clinical trial	59	NPI [12]
	Population-based	43	NPI [36]
		47	BSRS [11]
Depression	*Hospital-based*	9–78	NPI [30,32]
		53	CERAD-BRSD [31]
		36	CES-D [22]
		52	GDS [21]
		27 (minor)	DSM-IV [29]
		8–20 (major)	DSM-IV [22,29,31]
	GPs	15	GDS [33]
	Clinical trial	45	NPI [12]
	Population-based	16–46	NPI [11,36,37]
		36	CPRS [23]
		16–40	CES-D [17,19]
		63	GDS [40]
		2.4 (major)	DSM-IV [19]
Apathy	*Hospital-based*	11–53	NPI [30,32]
		40	CERAD-BRSD [31]
	GPs	NA	
	Clinical trial	32	NPI [12]
	Population-based	12–15	NPI [36,37]
		36	CPRS [23]
Anxiety	*Hospital-based*	11–74	NPI [30,32]
		49	CERAD-BRSD [31]
	GPs	NA	
	Clinical trial	45	NPI [12]
	Population-based	10–53	NPI [36,37]
		47	CPRS [23]
Delusions	*Hospital-based*	2–14	NPI [30,32]
		14	CERAD-BRSD [31]
	GPs	NA	
	Clinical trial	6	NPI [12]
	Population-based	0–3	NPI [36,37]
Hallucinations	*Hospital-based*	0–14	NPI [30,32]
		4	CERAD-BRSD [31]
	GPs	NA	
	Clinical trial	2	NPI [12]
	Population-based	1–9	NPI [36,37]
Agitation	*Hospital-based*	4–45	NPI [30,32]
		38	CERAD-BRSD [31]
	GPs	NA	
	Clinical trial	35	NPI [12]
	Population-based	5–11	NPI [36,37]
		25	BSRS [11]
Irritability	*Hospital-based*	13–53	NPI [30,32]
		36	CERAD-BRSD [31]
	GPs	NA	
	Clinical trial	44	NPI [12]
	Population-based	15–30	NPI [36,37]

Table 4, continued

Symptom	Study setting	Prevalence, %	Behavioral instrument [study reference]
Euphoria	*Hospital-based*	0–9	NPI [30,32]
	GPs	NA	
	Clinical trial	5	NPI [12]
	Population-based	1	NPI [36,37]
Disinhibition	*Hospital-based*	2–3	NPI [30,32]
	GPs	NA	
	Clinical trial	10	NPI [12]
	Population-based	3–7	NPI [36,37]
Aberrant motor behavior	*Hospital-based*	4–15	NPI [30,32]
	GPs	NA	
	Clinical trial	8	NPI [12]
	Population-based	1–4	NPI [36,37]

Abbreviations: NPI, Neuropsychiatric Inventory; NA, not available; BSRS, Behavioral Symptom Rating Scale; CERAD-BRSD, Consortium to Establish a Registry for Alzheimer's Disease Behavioral Rating Scale for Dementia; CES-D, Center for Epidemiological Studies Depression Scale; GDS, Geriatric Depression Scale; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; CPRS, Comprehensive Psychopathological Rating Scale.

havioral abnormalities in MCI [12,30,32,36,37]. The fourth and the fifth most common symptoms were apathy and agitation.

Hospital-based samples reported a higher global mean prevalence of any NPS than population-based studies (60% vs. 45% respectively). In particular, the former [30,32] described higher prevalence of nearly all NPS compared with the latter [36,37]. Data from the InDDEX trial reported NPS prevalence figures similar to those described by hospital-based studies [12].

With respect to NPS distribution in different MCI subgroups, only one hospital-based study evaluated the wide NPS spectrum in aMCI versus naMCI [32]. In this article, which reported the highest frequency of nearly all NPS described thus far, the authors demonstrated that aMCI displayed a higher frequency of depression, apathy, and irritability than naMCI, while the latter presented with a higher frequency of delusions and hallucinations than the former. Nevertheless, the two groups significantly differed only for hallucinations.

a) Depression: Depression is the most studied NPS in subjects with cognitive impairment, dementia, and AD [53,54]. Previous data have shown that depressive symptoms occurring more than 25 years prior to diagnosis are associated with an increased risk of developing AD, thereby suggesting that depression probably predisposes the brain to a later vulnerability to the disease [55,56]. Six hospital-based studies, 2 GP articles, the InDDEX trial, and 7 population-based studies have reported descriptive epidemiological features of depression in MCI.

Hospital-based studies

The prevalence of depressive symptoms ranged from 9% to 78% in MCI subjects attending hospital-based settings [21,22,29–32]. Five out of these 6 articles, which described the prevalence of depression in MCI, reported data collected in subjects attending memory clinics [21,22,29,31,32]; in the sixth article data were obtained from subjects receiving their routine medical care at the Mayo Clinic Division of Community Internal Medicine, subsequently referred to the Mayo Alzheimer's Disease Center [30]. Therefore, the prevalence figures of depression in MCI subjects directly attending memory clinics were higher than those reported by the study at the Mayo Clinic. In particular, MCI subjects directly attending memory clinics showed a prevalence of depressive symptoms ranging from 36% [22] to 78% [32] compared to 9% observed by the study of the Mayo Clinic [30]. This observed variability in symptom prevalence can also be accounted for by differences in MCI diagnostic criteria and the sensitivity of the behavioral instruments used. A further potential contributor to this discrepancy could be the exclusion of subjects with severe psychiatric conditions or those using psychotropic drugs from the sample identified by the study at the Mayo Clinic [30].

Gabrielewicz and collaborators [29] conducted a factor analysis with a varimax rotation to analyze the item scores from the Montgomery and Asberg Depression Rating Scale (MADRS) [44] in subjects with MCI. They found three partly independent depressive subsyndromes: one characterized by complaints about sadness; one characterized by predominant tension, anx-

iety, and concomitant vegetative symptoms; and one with decreased psychomotor activity. Three studies also described the prevalence figures of minor and major depression in their MCI samples according to DSM-IV criteria [22,29,31]. In particular, minor depression was observed in 27% of subjects [29], while the prevalence of major depressive episodes ranged from 8% to 20% of cases [22,29,31].

GP studies

The prevalence of depression was reported by two studies describing data from a large multicenter cross-sectional GPs study conducted in Germany [33,34]. The study sample included 818 MCI subjects, and depression was assessed by the Geriatric Depression Scale (GDS) [45]. In one of these studies [33], the prevalence of depression in MCI subjects was 13%. In a subsequent analysis of the same sample [34], the authors detailed specific prevalence figures of depression among different MCI subtypes. In particular, depression was found in 16% of subjects with single-domain aMCI, 9% with single-domain naMCI, 19% with multi-domain aMCI and 18% with multi-domain naMCI.

Clinical trial and population based-studies

The InDDEX trial [12] described baseline data of 1,010 aMCI subjects evaluated using the NPI. The InDDEX trial systematically excluded subjects with no or very mild depressive symptoms as well as those with a DSM-IV diagnosis of major depression. The prevalence of depressive symptoms in the InDDEX trial was over 45% [12].

Sixteen to 63% of MCI subjects were enrolled in population-based studies characterized by depressive symptoms [11,17,19,23,36,37,40]. The results were somewhat different between the studies, probably due to the use of different behavioral instruments to assess depression. In particular, Solfrizzi et al. [40] detailed the highest prevalence of depressive symptoms among MCI subjects reported thus far from population-based studies. Indeed, they observed depressive symptoms in 63% of their MCI subjects evaluated with the GDS. One study also described that 2.4% of their MCI sample suffered from current major depressive episodes [19], which were assessed using the Major Depressive Episode module of the Mini International Neuropsychiatric Interview (MINI) [52], according to DSM-IV criteria.

b) Apathy: Apathy has been reported as the most frequent NPS in subjects with dementia and AD [53,

54]. It commonly starts with a mild dementia stage and progressively increases in frequency with progressing dementia [53]. Three hospital-based studies, the InDDEX trial and 3 population-based studies have described the prevalence figures of apathy in MCI.

Hospital-based studies

Substantially similar prevalence estimates of apathy in MCI subjects were reported in the studies of Lopez et al. (40%) [31] and Rozzini et al. (53%) [32], despite the use of different behavioral instruments to evaluate the presence/absence of apathy. In contrast, the authors in the Mayo Clinic study reported a rather low prevalence of apathy (11%) [30]; the potential reason for this variability was described above (see section "Depression: Hospital-based studies"). In the Mayo Clinic study, apathy was the second most common symptom of MCI subjects [30], while it was the third most prevalent symptom after depression and anxiety in the two other studies [31,32].

Clinical trial and population based-studies

The prevalence of apathy reported by the InDDEX trial in MCI subjects assessed with the NPI was over 32% [12]. A similar figure was obtained by examining population-based data from the Kungsholmen Project, a Swedish population-based cohort study [23]. Indeed, in this study the authors, using the Comprehensive Psychiatric Rating Scale (CPRS) [50], reported motivation-related symptoms in 36% of MCI subjects. In contrast, data from two other NPI-based studies conducted at a population level reported a prevalence figure of apathy of MCI ⩽15% [36,37]. Apathy was the second most common behavioral symptom in MCI subjects in two population-based studies [23,36], while it was fourth in the InDDEX trial [12] and in a Thai community-based study [37].

c) Anxiety: Anxiety has been reported as the third most common NPS in subjects with AD after apathy and depression [53]. However, as a behavioral symptom, it is difficult to evaluate in the elderly as separating a medical condition from the physical symptoms of an anxiety disorder is rather difficult in old age [57]. Furthermore, diagnosing anxiety in individuals with dementia can be particularly complex, and, indeed, agitation typical of dementia may be confused with anxiety [57]. Three hospital-based studies, the InDDEX trial and 3 population-based studies have investigated anxious symptoms in MCI.

Hospital-based studies

There was a substantial discrepancy in the prevalence rates of anxiety reported by the 3 hospital-based studies conducted on MCI subjects thus far [30–32]. Two NPI-based studies described rather different prevalence rates of anxiety in MCI: 11% in the article by the Mayo Clinic [30] versus 74% in that by Rozzini et al. [32]. Using the Consortium to Establish a Registry for Alzheimer's Disease Behavioral Rating Scale for Dementia (CERAD-BRSD) [49], Lopez and colleagues [31] diagnosed anxiety in 49% of their MCI sample. Again, this discrepancy may be due to different sampling methods, MCI diagnostic criteria, and behavioral instruments used. Anxiety was the second most common behavioral symptom among MCI subjects in the 3 hospital-based studies, after depression [31,32] and irritability [30] respectively.

Clinical trial and population based-studies

The InDDEX study reported a very high prevalence of anxiety (45%) among subjects included in their large clinical trial of MCI subjects [12]. With reference to studies conducted at a population-level in subjects with MCI, data from two NPI-based studies described anxiety in 10% [36] and 53% [37] of their cohorts respectively. Similar to the latter, the CPRS-based data from the Kungsholmen Project reported a prevalence of anxiety of 47% among MCI subjects [23]. Of interest, anxiety was the most common behavioral symptom among MCI subjects in two population-based studies [23,37], while it was the second in the InDDEX trial [12] and the fourth in the Cardiovascular Health Study's (CHS) Cognition Study [36], a large multicenter population-based cohort study.

d) Delusions and hallucinations: Psychotic symptoms are common and persistent features in patients with AD, leading to a faster rate of cognitive decline, excess disability, and early institutionalization [58]. They were also described as independent risk factors for cognitive impairment in non-demented subjects [5]. Three hospital-based studies, the InDDEX trial and 3 population-based studies have reported prevalence rates of psychotic features in MCI.

Hospital-based studies

The two NPI-based studies described a very low frequency of psychotic symptoms in MCI subjects, ranging from 2% to 14% for delusions and 0% to 14% for hallucinations [30,32]. Of interest, Rozzini and colleagues [32] observed a significantly higher frequency

of hallucinations in naMCI (23%) compared to aMCI (4%). Using the CERAD-BRSD, Lopez et al. [31] reported the prevalence of hallucinations and delusions among their MCI subjects to be 4% and 14% respectively.

Clinical trial and population based-studies

The InDDEX trial and two population-based studies used the NPI to evaluate the frequency of delusions and hallucinations in MCI subjects [12,36,37]. The InDDEX study described frequency rates of 6% for delusions and 2% for hallucinations [12]. The CHS Cognition Study reported very low prevalence rates of delusions (3%) and hallucinations (1%) in MCI subjects [36]. Similarly, Muangpaisan et al. [37] identified prevalence rates of 0% for delusions and 9% for hallucinations. Finally, Chan et al. [11] in a small population-based study of 121 MCI subjects reported a global prevalence of psychosis of 9% using the Behavioral Symptom Rating Scale (BSRS) [48].

e) Agitation: Prevalence rates of agitation in MCI were described by 3 hospital-based studies, the InDDEX trial, and 3 population-based studies. Despite the use of different behavioral instruments, similar prevalence estimates of agitation in MCI subjects were reported by the hospital-based studies of Lopez et al. (38%) [31] and Rozzini et al. (45%) [32]. In contrast, the authors in the Mayo Clinic study reported the lowest prevalence of agitation (4%) described thus far in MCI [30]; in the InDDEX trial the frequency of agitation was 35% [12]. Prevalence rates of agitation, as measured by the NPI among MCI subjects enrolled in population-based studies, ranged from 5% in the article by Muangpaisan et al. [37] to 11% in the CHS Cognition study [36]. Using the BSRS, the population-based study by Chan et al. [11] found the prevalence of agitation among MCI to be 25%.

f) Irritability: Three hospital-based studies, the InDDEX trial, and 2 population-based studies reported prevalence figures of irritability in MCI. The two hospital-based studies which used the NPI observed prevalence rates of irritability ranging from 13% in the Mayo Clinic study [30] to 53% in the article by Rozzini et al. [32]. Using the CERAD-BRSD, Lopez and colleagues [31] found the frequency of irritability among MCI to be 36%. The InDDEX trial reported the highest prevalence of irritability (44%) described thus far in MCI [12]. NPI-based studies conducted at a population levels described prevalence rates of irritability among

MCI subjects which ranged from 15% in the CHS Cognition Study [36] to 30% in the article by Muangpaisan et al. [37].

g) *Euphoria, disinhibition and aberrant motor behavior:* Two hospital-based studies, the InDDEX trial, and 2 population-based studies, all using the NPI, have detailed prevalence rates of euphoria, disinhibition, and aberrant motor behavior in MCI subjects. In hospital-based studies the frequencies of euphoria, disinhibition, and aberrant motor behavior were 0–10%, 2–3%, and 4–15% respectively [30,32], while the InDDEX trial reported the highest prevalence of these three NPS described thus far in MCI [12]. Lastly, in population-based MCI cohorts, the frequencies of euphoria, disinhibition, and aberrant motor behavior were 1%, 3–7%, and 1–4% respectively [36,37].

2. Incidence of NPS in MCI

Only one study has reported incidence figures of NPS in subjects with MCI. In particular, Solfrizzi and colleagues [40] described incidence rates of depressive symptoms in MCI subjects enrolled in the Italian Longitudinal Study on Aging (ILSA) and prospectively followed during a 3.5-year period using the GDS. Thirty-six out of the 139 baseline MCI subjects were examined at follow-up for possible new onset of depressive symptoms. During the 3.5-year follow-up period, all 36 MCI subjects developed a new onset of depressive symptoms, with an estimated incidence rate of 29.6 per 100 person-years. No socio-demographic variables or vascular risk factors modified the incidence of depressive symptoms in cognitively stable MCI patients or in MCI patients who reverted to normal cognition.

3. Associated factors of NPS in MCI

Three hospital-based studies, the InDDEX trial, and 2 population-based studies described the cross-sectional, associated factors of NPS in MCI. Rozzini et al. [14] used data from 150 MCI outpatients to establish whether NPS are associated with mild parkinsonian signs. The authors used the Unified Parkinson Disease Rating Scale-motor section [59] to define the presence of mild parkinsonian signs, while NPS were evaluated using the NPI. The MCI group with mild parkinsonian signs had a significantly higher prevalence of depression, apathy, and anxiety compared to the MCI group not characterized by parkinsonian signs.

Hudon and collaborators [13] examined executive as well as memory functioning in 44 subjects with aMCI, referred to an outpatient memory clinic. The aMCI subjects were distinguished according to the presence or absence of subclinical depressive symptoms using the GDS. Compared to the non-depressed aMCI group, the depressed aMCI group displayed impaired executive functions, while the two groups did not substantially differ with regard to their verbal episodic memory. In another hospital-based study, Bruce et al. [28] explored the relationship between cognitive functioning and self-reported depression in 82 subjects with MCI evaluated with the Beck Depression Inventory [43]. They found that poorer memory functioning was associated with fewer self-reported depressive symptoms. In addition, aMCI reported fewer symptoms of depression than naMCI subjects. The authors hypothesized, consistent with that observed in AD patients [60], that subjects with MCI may have difficulty reporting their psychiatric symptoms due to problems of recall.

The association between NPS and cognitive functioning was also evidenced by the InDDEX trial [12]. In this study subjects scoring $\geqslant 1$ on the NPI had significantly lower scores on measures of global cognition compared to subjects without NPS. Furthermore, the former reported lower scores on functional measures than the latter. The association between functional difficulties and NPS in MCI was also reported by the population-based study by Chan et al. [11]. After multivariate logistic regression analysis, the authors found that the presence of any NPS symptoms, assessed using the BSRS, was significantly associated with difficulties in basic as well in the instrumental activities of daily living. Another small population-based study was conducted on the Thai population to investigate the pattern of NPS in 77 MCI subjects and the influence of socio-demographic factors on these symptoms [37]. The authors found that depression and anxiety, evaluated using the NPI, were associated with self-reporting of belonging to a low-status economic group.

4. NPS as risk factors/predictors for MCI and conversion to dementia and AD

Thirteen studies evaluated the role of NPS as putative risk factors for MCI or as predictors for the conversion from MCI to dementia and AD, using prospective cohort studies. In particular, 5 hospital-based studies, the clinicopathological study of older Catholic clergy, and 7 population-based studies addressed this issue. 11 out of these 13 articles evaluated depression as a risk

factor/predictor for MCI or its development to dementia [15–22,35,38,39], one reported that anxiety symptoms predict conversion from MCI to AD [23], and the latter found depression and apathy were more common in subjects who were later diagnosed with AD [24].

With reference to hospital-based studies, Modrego and Ferrández [22] followed a cohort of 114 aMCI subjects over a mean period of 3 years. At baseline examination, depression evaluated by the GDS was observed in 36% of subjects. After a mean period of 3 years depressed MCI were 2.6 times more likely to develop dementia in comparison with non-depressed MCI. Of interest, the survival analysis showed that depression predicts a faster cognitive deterioration in MCI subjects. Furthermore, a poor response to antidepressant therapy was seen in converters compared to nonconverters, thus suggesting that depression secondary to AD pathology is persistent and possibly refractory to therapy. Gabryelewicz and colleagues [20] assessed 105 patients with MCI over 3 years to investigate the risk of the conversion of single aMCI versus multiple-domain aMCI to dementia and to identify if depression predicts this conversion. The authors found that 22% of MCI patients developed dementia and that depressive symptoms at baseline, as evaluated by the MADRS, predicted a greater risk for developing dementia. Houde et al. [21] evaluated 60 aMCI subjects attending a memory clinic using the GDS for an average period of 4.3 years. They found that the simple presence or absence of depression at referral did not predict the progression of MCI to AD. In contrast, the positive answers to specific GDS items (i.e., those related to *melancholic* depressive features) as well as the persistence of depression over two to three years significantly predicted conversion from MCI to AD.

In another large hospital-based, prospective cohort study, Geda et al. [16] reported a synergistic interaction between the apolipoprotein E4 (ApoE4) genotype and depression in increasing the risk of aMCI. They followed 840 initially cognitively normal and depression-free individuals over a median of 3.5 years and found that those who developed depression experienced double the risk of subsequently developing aMCI. Those subjects, who had recently developed depression (i.e., no past medical history of depressive episodes), displayed a hazard ratio (HR) for cognitive decline of 4.5 (95% confidence intervals [CI], 1.9–10.9), compared to those who were never depressed. This suggests a protective effect of antidepressant medications in subjects with a previous history of depression. There was an additive interaction between depression and ApoE4

in increasing the risk of developing aMCI (HR, 5.1; 95% CI, 1.9–13.6). In the study by Teng and collaborators [24], the authors evaluated NPS using the NPI in 51 subjects with aMCI and naMCI attending memory clinics. Over a mean 2.0 years of follow-up, they found that depression (67 vs. 31%) and apathy (50 vs. 18%) were significantly more common in MCI subjects who were later diagnosed with AD, suggesting that some NPS may be independently associated with the progression from MCI to AD.

Several population-based studies confirmed the role of NPS, particularly depression, as a risk factor for MCI or its conversion to dementia. Lopez et al. [17] examined risk factors for the development of MCI over a mean period of 5.8 years in 2,895 participants of the CHS Cognition Study. Of the several risk factors investigated, depressive symptoms – which were evaluated using the Center for Epidemiological Studies Depression Scale (CES-D) [42] – were significantly associated with the development of MCI (Odds ratio [OR],1.5; 95% CI, 1.2–2.0). Another study used data from the CHS Cognition Study to establish whether depressive symptoms at baseline predicted an increased risk of MCI over 6 years [15]. Depression, as evaluated by the CES-D, was associated with an increased risk of MCI, and this was correlated with the severity of baseline depression. Interestingly, adjusting for several vascular diseases (including carotid artery atherosclerosis measured using duplex ultrasonography and cerebral infarcts and white matter disease evaluated by magnetic resonance imaging) had little effect, suggesting that this association was independent of the presence of any underlying vascular disease.

The Three City Study [19], a multi-site prospective cohort study of community-dwelling people conducted in three French cities, examined 6,892 participants of which 2,879 were diagnosed with MCI at baseline during a 4-year period; depression was assessed by the CES-D. The study reported that subclinical depression was independently associated with the progression of MCI to dementia only in women (OR, 2.0; 95% CI, 1.1–3.6), suggesting that the two sexes possess different risk profiles for this conversion. In the study by the Kungsholmen Project [23], the role of mood-, motivation- and anxiety-related symptoms were evaluated in 47 MCI subjects who were followed for a mean of 3 years as predictors for the progression from MCI to AD. They found that the 3-year risk of progression to AD almost doubled with each anxiety symptoms in subjects with MCI (relative risk [RR], 1.8; 95% CI, 1.2–2.7). In contrast, mood-related symptoms predict

conversion to AD in cognitively-intact subjects (RR, 1.9; 95% CI, 1.0–3.6). Accordingly, the authors suggested that anxiety symptoms in MCI may represent a subjective reaction to the initial phase of cognitive deterioration, while mood-related symptoms may be related to AD pathology, thus representing preclinical signs of the disease. Another study, which analyzed data from the Canadian Study of Health and Aging [18], evaluated the role of NPS as predictors for the conversion from normal cognition to MCI as well as for the progression from MCI to dementia and AD. A nationwide population-based study was used in which data were collected 3 times at 5-year intervals; NPS were evaluated using section H of the Cambridge Examination for Mental Disorders of the Elderly [51]. When checking for initial cognitive status, loss of interest and depression significantly contributed to the prediction of MCI, dementia, and AD.

In contrast to the aforementioned data, three studies did not report depression as a risk factor for AD or a predictor for its conversion to dementia and AD. The Religious Order Study [35], a clinicopathological study of older Catholic clergy, followed 917 older Catholic nuns, priest, and monks without dementia at study entry for up to 13 years, who were then evaluated annually; depression was evaluated with the CES-D scale. Trajectories of depressive symptoms prior to (mean follow-up of 3.2 years) and after (mean follow-up of 3.9 years) the development of incident MCI were estimated. There was no systematic change in depressive symptoms before or after the initial MCI diagnosis, thus suggesting the depressive symptoms do not increase in the prodromal phase of AD.

Similarly, data from the ILSA study suggested that depressive symptoms, evaluated using the GDS, represent neither a risk factor for incident MCI nor predictors for its progression to dementia [38,39]. As previously mentioned, these differences may be due to the different enrollment criteria for the MCI cohort.

DISCUSSION

Our systematic review of previously published data has revealed that NPS are very prevalent in subjects with MCI. They may represent risk factors for MCI or predictors for the conversion of MCI to dementia and AD. According to these data, we believe it is important to recognize and treat NPS early on in subjects with MCI because this comorbidity can be associated

with worse cognitive performance, mild extrapyramidal signs, and functional disability [11–14].

Concerning descriptive epidemiological features, the global prevalence of NPS in MCI ranges from 35% to 85% [11,12,30,32,36], with a similar pattern of symptoms, albeit with reduced frequency, compared to dementia and AD [53,54]. In particular, the most common behavioral symptoms are (in order of frequency): depression, anxiety, irritability, apathy, and agitation, while less frequent symptoms are euphoria, disinhibition, delusions, and hallucinations [12,30,32,36, 37]. Hospital-based samples [30,32] described a higher global prevalence of NPS than population-based studies [36,37], probably reflecting selection bias (i.e., persons attending memory clinics tend to report NPS with higher frequency because their own symptomatology is more serious than subjects evaluated at a population level).

Only one hospital-based study has evaluated the wide NPS spectrum in aMCI versus naMCI [32]. Subjects with aMCI presented with higher frequency mood-related features (i.e., depression and apathy) and irritability than naMCI; in contrast, the latter displayed more numerous psychotic-related features (i.e., delusions and hallucinations) than the former. If confirmed, this differential behavioral profile of aMCI versus naMCI subjects may be valuable in offering prognostic information as there is preliminary evidence that the two conditions display differing outcomes [1,3]. There has been a single study reporting the incidence figures of NPS in MCI [40]. Over a 3.5 year follow-up period, the authors estimated an incidence rate of depressive symptoms of 29.6 per 100 person-years. Incidence rates of depressive symptoms were not modified by sociodemographic variables or vascular risk factors.

Differences in the prevalence of NPS between data reviewed in this study may depend upon several factors. Firstly, differences in study setting (hospital vs. population study) may have led to a selection bias. Secondly, differences in age and sex distribution within the studies may have also caused differences in reported prevalence figures. Indeed, it has been reported that the prevalence of depression increases with age in cognitively impaired subjects [9] and its related features (i.e., mood- versus motivation-related symptoms) vary with sex in the elderly [61], being higher in females than in males. Thirdly, inclusion and exclusion criteria may have affected reported prevalence figures. For example, using $\geqslant 1.0$ SD versus $\geqslant 1.5$ SD below age and education-adjusted scores as cut-off points for diagnosing cognitive impairment may have led to an in-

crease in the size of MCI in a specific cohort. However, this group will probably possess less cognitive deficits compared to those cohorts using the 1.5 SD cut-off point with inherent reflections on the prevalence of NPS. Regarding exclusion criteria, the exclusion of subjects with depressive symptoms or those using psychotropic drugs [12,13,16,20,29,30,37] may have affected the prevalence not only of depression itself but also of other comorbid NPS, due to the fact that the former is often comorbid with the latter (e.g., apathy and anxiety) [62,63].

Lastly, discrepancies in prevalence rates between studies may be due to the differential sensitivity of instruments used for evaluating NPS in MCI. Indeed, various instruments have been specifically developed to evaluate behavioral and psychological symptoms in subjects with cognitive impairment and dementia (e.g., NPI, BSRS) [47,48], while others represent global measures of psychiatric symptomatology, developed for adults and then applied to elderly subjects (e.g., CPRS, MINI) [50,52]. Furthermore, subjects with MCI-developing-dementia may have various mild problems of insight, memory, and verbal expression, causing difficulty in providing reliable self-report information relating to their behavioral profile [60]. Thus, the use of a caregiver report to assess a subject's behavioral status often provides more information [64].

With reference to analytic epidemiological features, NPS in MCI are associated with worsening cognitive performance [12,13], functional disability [11,12], mild extrapyramidal signs [14], and poor economic status [37]. Furthermore, depression is associated with an increased risk of developing MCI [15–18]. Of interest, Geda and colleagues [16] have described a synergistic interaction between depression and the ApoE4 genotype in increasing this risk, thus suggesting that depression could lead to cognitive impairment in the presence of a specific genetic susceptibility factor. Lastly, baseline levels of depression, apathy and anxiety were also associated with an increased risk of conversion from MCI to dementia and AD [18–24]. Notably, data from one of these studies revealed that MCI subjects with a poor response to antidepressant therapy are at increased risk of developing dementia [22]. Globally, these data suggest that NPS in MCI subjects could serve as clinical indicators for the presence of prodromal dementia; the lack of responsiveness to antidepressant treatment strengthens this issue [22]. In contrast, recent data from a clinicopathological study of older Catholic clergy [35] as well as those by the ILSA study [38, 39] did not report depressive symptoms as a risk factor

for MCI or as a predictor for progression from MCI to dementia. Contrasting findings between these studies and data reported above can probably be accounted for by differences in study setting, demographics, MCI diagnostic criteria, and the sensitivity of the behavioral instruments used.

The strengths of this systematic review are the use of strict inclusion criteria for study selection in attempting to limit the heterogeneity of analyzed data. Furthermore, we used standardized procedures for extracting data from included studies. However, various methodological issues deserve mentioning: first, we only evaluated studies in English; and second, the heterogeneity in the population study settings, diagnostic criteria for MCI, and various instrument for NPS assessment affected our ability to compare data from different studies. One previous systematic review relating to this topic has recently been published [10]. However, it summarizes findings published before December 2006, it used neither strict inclusion criteria for MCI diagnosis nor did it address duplicate publication.

Overall, it seems clear that NPS and MCI often co-occur in the elderly, and that mood-related and anxiety symptoms are frequently prodromal to MCI and dementia. Since neuropathological signs of cognitive impairment and dementia precede clinical symptoms by many years [65,66], the direction of causality is not clear: NPS may reflect specific pathological changes in the brain or indicate a subjective reaction to cognitive changes. Furthermore, in some cases NPS can mask the detection of *true* MCI, while only reflecting the presence of an underlying behavioral disorder rather than the product of a dementia-related illness. This kind of *psychogenic* MCI could at least partly justify the significant rate of reversion from MCI to normal cognition and functioning, observed by population-based studies [6,7]. Accordingly, the clinician must endeavor to distinguish primary behavioral changes from cognitive impairment, by firstly attempting to initiate specific treatment for mood changes then, possibly, evaluating and treating the cognitive disorder.

This review reveals that NPS are highly prevalent in MCI. Furthermore, NPS increase the risk of developing MCI and/or its future conversion to dementia. Due to the highly heterogeneous data on NPS in MCI to date, large cohort studies using standardized MCI criteria and behavioral instruments are required to evaluate the prognostic role of NPS in MCI; within this context subjects with depression at baseline should not be excluded. Recently proposed directions for future research on this issue include [9]: evaluating the prevalence,

correlates and predictive validity of NPS in different MCI subtypes; refining and developing approaches to specifically assessing NPS in subjects with MCI; and identifying genetic and biological markers linking NPS to MCI and dementia. Lastly, the role of vascular risk factors in mediating the relationship between NPS and MCI should be detailed [67]. Taking these factors into consideration, all this information would make a significant contribution to enhancing treatment strategies for subjects with MCI.

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