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Neuropsychiatric symptoms as early manifestations of emergent dementia: Provisional diagnostic criteria for mild behavioral impairment

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Abstract

Neuropsychiatric symptoms (NPS) are common in dementia and in predementia syndromes such as mild cognitive impairment (MCI). NPS in MCI confer a greater risk for conversion to dementia

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in comparison to MCI patients without NPS. NPS in older adults with normal cognition also confers a greater risk of cognitive decline in comparison to older adults without NPS. Mild behavioral impairment (MBI) has been proposed as a diagnostic construct aimed to identify patients with an increased risk of developing dementia, but who may or may not have cognitive symptoms. We propose criteria that include MCI in the MBI framework, in contrast to prior definitions of MBI. Although MBI and MCI can co-occur, we suggest that they are different and that both portend a higher risk of dementia. These MBI criteria extend the previous literature in this area and will serve as a template for validation of the MBI construct from epidemiologic, neurobiological, treatment, and prevention perspectives.

Keywords

Dementia; FTD; Alzheimer's disease; MCI; MBI; Neuropsychiatric symptoms of dementia; NPS; Behavior; Behaviour; Agitation; Psychosis; Disinhibition; Apathy; Depression; BPSD

1. Background

1.1. Neuropsychiatric symptoms of dementia, mild cognitive impairment, and normal cognition

Neuropsychiatric symptoms (NPS) of dementia are common and of increasing interest to clinicians and researchers. NPS are the noncognitive or behavioral and psychiatric symptoms of dementia and include disturbances of mood, perception, and behavior associated with neurodegenerative disease [1]. NPS in dementia are associated with poorer outcomes including greater caregiver burden [2], greater functional impairment [3], higher rates of institutionalization [4], poorer quality of life [5], accelerated progression to severe dementia or death [6], and higher burden of neuropathologic markers of dementia [7]. Furthermore, NPS are present in the prodromal or mild cognitive impairment (MCI) stages of dementia, with one study reporting them in 59% of subjects enrolled in a large MCI clinical trial; furthermore, these individuals with NPS had greater impairment on global, cognitive, and functional scores than those without NPS [8]. Large sample longitudinal studies provide further evidence that NPS in MCI increase risk of dementia. In an analysis of National Alzheimer's Coordinating Center (NACC) data, the presence of NPS increased the incidence of dementia (hazard ratio [HR] = 1.37, 95% confidence interval [CI] = 1.17–1.84), with an estimated annual conversion rate of 25% for MCI comorbid with NPS [9]. Similarly, the population-based Cache County study identified NPS, even of mild severity, as a risk factor for conversion from cognitive impairment no dementia to all-cause dementia [10]. The 2011 National Institute on Aging–Alzheimer's Association (NIA-AA) consensus recommendations for diagnosis of all-cause dementia have included behavioral symptoms by modifying the core criteria to add "changes in personality, behavior, or comportment—symptoms include uncharacteristic mood fluctuations such as agitation, impaired motivation, initiative, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive or obsessive behaviors, socially unacceptable behaviors" [11]. Inclusion as core criteria provided an emphasis on the importance of NPS in neurodegenerative disease.

Evidence suggests that even subtle NPS in cognitively normal adults can predict cognitive decline. Pietrzak et al. [12] described the predictive nature of “mild worry” symptoms for cognitive decline at 2-year follow-up in a group of 263 cognitively intact older adults. These “mild worry” symptoms did not meet threshold criteria for an anxiety disorder and yet were important predictors of cognitive decline in the domains of visual learning and memory compared with older adults with “minimal worry” at baseline. The population-based Mayo Clinic Study of Aging highlighted the importance of NPS in cognitively normal older adults (age ≥70 years). The presence at baseline of NPS such as agitation (HR = 3.06, 95% CI = 1.89–4.93), apathy (HR = 2.26, 95% CI = 1.49–3.41), anxiety (HR = 1.87, 95% CI = 1.28–2.73), irritability (HR = 1.84, 95% CI = 1.31–2.58), or depression (HR = 1.63, 95% CI = 1.23–2.16) increased the risk of developing MCI in comparison to participants without NPS at baseline [13]. In comparison, biomarker analysis from the Mayo Clinic Study of Aging estimated that hippocampal atrophy (by magnetic resonance imaging) increased the risk of incident MCI to a lesser degree than four of the five aforementioned NPS (HR = 1.8, 95% CI = 1.4–2.20) [14], affirming the clinical relevance of NPS in comparison to other well-established predictors of conversion from MCI to dementia. Data have continued to emerge in support of the notion of NPS manifesting in advance of cognitive impairment for neurodegenerative disease. Donovan et al. [15] studied 559 participants who were cognitively normal, had subjective cognitive concerns, or who had MCI, from the Massachusetts Alzheimer’s Disease Research Center Longitudinal Cohort. Greater symptoms of depression, irritability, and agitation predicted more rapid progression to a worse diagnosis across all groups, including the cognitively normal. The authors state “these findings support a model of Alzheimer’s Disease (AD) in which cognitive and neuropsychiatric alterations are measurable before the stage of MCI and offer potential to enhance early detection and intervention.” Banks et al. [16] assessed 644 cognitively healthy older subjects from the Alzheimer’s Disease Cooperative Study (ADCS) Prevention Instrument Project. Over the 4-year follow-up, baseline symptoms of anxiety and depression (measured cross-sectionally with the NPI) predicted conversion to Clinical Dementia Rating (CDR) ≥0.5. The authors state “early anxiety and depression may be the harbingers of future cognitive decline, and that patients exhibiting such symptoms, even in the absence of co-occurring cognitive symptoms, should be closely followed over time.” Masters et al. [17] used NACC data from 2416 cognitively normal participants more than 50 years of age to describe the predictive nature of incident NPS on conversion from CDR =0 to CDR >0. The authors found a significantly earlier presence of NPS in cognitively normal patients who subsequently developed a CDR >0. They described the initial phase of “noncognitive” AD as irritability, depression, and nighttime behavior changes, followed by anxiety, appetite changes, agitation, and apathy symptoms. These NPS were simply cross-sectionally captured at baseline and yet still proved to be powerful predictors of development of cognitive impairment. Thus, an ever increasing body of evidence describes NPS in older adults as potentially early markers of cognitive decline and progression along the neurodegenerative spectrum.

1.2. Neurobiology of NPS

Inasmuch as neurodegeneration contributes to the cognitive symptoms of dementia, current understanding of NPS supports an etiologic role of neurodegeneration in the manifestation

of behavioral and psychological symptoms as well. Alexander [18] initially described frontal-subcortical circuitry and suggested both motor and other “complex” behaviors may be associated with damage to these regions. In synthesizing degeneration and lesion literature, Cummings [19] described the role of frontal-subcortical circuits in human behavior and the impact of circuit disruption in generating motor symptoms as well as apathy, depression, mania, and obsessive compulsive disorder. Basal ganglia lacunae have been shown to contribute to depression, delusions, and hallucinations in AD patients, independent of the AD process [20]. Neurodegenerative disease and vascular burden contribute to the manifestation of NPS in dementia such as agitation [21], anxiety [22], apathy [23], appetite change [24], delusions [25], depression [26], disinhibition [27], moria (childish excitement or frivolous behavior) [28], and sleep disturbance [29].

1.3. NPS as early manifestations of frontotemporal dementia and the genesis of the MBI concept

It has long been recognized that behavioral symptoms are an early manifestation of frontotemporal dementia (FTD) [30]. The International Behavioral Variant FTD Criteria Consortium revised FTD criteria for possible behavioral variant FTD (bvFTD) describe, “progressive deterioration of behavior and/or cognition by observation or history” [31]. The criteria include behavioral disinhibition, apathy, inertia, loss of sympathy or empathy, perseverative, stereotyped or compulsive/ritualistic behavior, hyperorality, and dietary changes which are persistent or recurrent [31]. Other less frequent presentations of bvFTD have been described including pathologic gambling [32] and hyperreligiosity [33]. It was in this context of early FTD that the first criteria for MBI were proposed by Taragano et al. [34,35] (Table 1). These criteria were proposed to identify FTD patients earlier in the course of the illness, although criterion (2) “no serious memory complaints” left it open whether patients had concurrent MCI. These MBI criteria served to describe a neuropsychiatric prodrome to FTD in advance of significant memory decline.

In a review of FTD, Hallam et al. [36] suggested three approaches to understand its prodromal syndrome: (1) cognitive profiling, (2) presence of behavioral/psychiatric symptoms in the absence of memory complaints, and (3) combination of cognitive, behavioral, and neuroimaging features. The approach of cognitive profiling builds on Petersen’s MCI criteria [37]. This approach suggests that nonamnestic single domain MCI may be a precursor to FTD and, while executive dysfunction is common to other dementia prodromes, when appearing in isolation, it may be more specific to bvFTD [38]. However, longitudinal data have demonstrated lack of specificity in this approach. Busse et al. [39] empirically validated the MCI subtypes in a longitudinal study of community dwelling older adults. Although persons with nonamnestic single domain MCI converted to non-AD dementias at a higher rate than those with amnestic MCI, this group was also the most likely to improve over the course of the follow-up period. The approach of combined behavioral/psychiatric symptoms in the absence of memory complaints was described by Scholzel-Dorenbos [40]. Using the Taragano criteria, three cases were described in which patients presented with psychiatric and behavioral symptoms not meeting FTD criteria, but who met MBI criteria. All three patients had nonmemory domain cognitive impairment and single photon emitted computer tomography findings of frontotemporal hypoperfusion. De

Mendonca et al. [41] extended this thinking and combined cognitive, behavioral, and neuroimaging criteria to propose frontotemporal MCI (FT-MCI) criteria consisting of frontotemporal dysfunction, frontal cognitive impairment, maintenance of function plus neuroimaging findings that were either normal or consistent with frontotemporal atrophy (Table 2). These criteria were retrospectively applied to a clinical population of 103 cases diagnosed with MCI, age-associated memory impairment, FTD, or frontal syndrome. Seven met the proposed FT-MCI criteria and six of these were diagnosed with FTD in 1.8 ± 1.0 years. However, five of the seven patients had frontal or frontotemporal atrophy at the time of FT-MCI diagnosis, suggesting relatively advanced disease progression at that time. Thus, although all approaches may have been helpful to diagnose incipient FTD, patients with behavioral symptoms in the absence of cognitive symptoms were still not captured in these frameworks. Thus, there remained a need for an approach to capture incipient dementia in the absence of clear cognitive impairment.

1.4. NPS as early manifestations of other dementias

Although common in FTD, NPS can be an early manifestation of other dementias. In the original Taragano study, a series of patients with NPS as the presenting complaint in advance of cognitive impairment were followed for 3 years. At the end point, 36% had FTD, 28% had AD. 18% had vascular dementia (VaD), and 18% had other types of dementia suggesting that any of the dementia syndromes can first present only with behavioral symptoms [34]. In a series of 252 consecutive specialty clinic patients, Wool1ey et al. [42] found that 28.2% of patients with a neurodegenerative illness first received a psychiatric diagnosis with depression being the most common. Although 52.2% of patients with bvFTD received a prior psychiatric diagnosis, patients with other dementias also received psychiatric diagnoses before neurodegenerative ones including 23.1% of those ultimately diagnosed with AD.

1.5. Rationale for new MBI criteria

One rationale for developing new MBI criteria is to define more clearly the relationship between MBI and MCI. Until now, the degree to which cognitive impairment is present within MBI patients has not been well defined or operationalized. Furthermore, the concept of MBI needs to be studied in the context of all dementia types, despite its origins in attempting to predict incipient bvFTD, with clear operationalized criteria. Identifying the MBI population is also a novel approach to studying prevention, with the hypothesis that early identification and treatment of behavioral symptoms in neurodegenerative illness may slow or mitigate the presentation of cognitive symptoms or that using MBI criteria to assist in early identification of neurodegenerative illness may allow for future disease-modifying agents to be used promptly. Standardizing the assessment of MBI will help define a target population for treatment studies. Identifying NPS early in the neurodegenerative process may allow for development of new treatments or assess potentially greater efficacy for older treatments. Finally, there is scientific interest in furthering knowledge of brain-behavior relationships by studying NPS syndromes caused by neurodegenerative disease.

2. Diagnostic criteria

2.1. Criteria development and search strategy

Initial discussion around the need for new MBI criteria stemmed from the annual meeting of the NPS Professional Interest Area (PIA) of the International Society to Advance Alzheimer's Research and Treatment (ISTAART) at the Alzheimer's Association International Conference (AAIC) 2012 in Vancouver, Canada. Chaired by authors C.G.L. and D.M., the NPS-PIA is an international, interdisciplinary group focused on defining clinical entities that will serve as targets for research and treatment development in later years. The NPS-PIA includes working groups related to specific NPS in AD, namely depression, agitation, apathy, psychosis, and sleep disorders. A working group was formed in 2012 to develop MBI criteria, headed by author Z.I.

In developing the criteria, in addition to reviewing the initial Taragano conference proceedings and articles, Pubmed and Medline searches were performed with search criteria "mild behavioral impairment," "MBI," "prodromal dementia," "neuropsychiatric symptoms of dementia," "non-cognitive symptoms of dementia," "NPS," "behavioral and psychological symptoms of dementia," and "BPSD". Both the American and UK spelling of "behavior/behaviour" were used in the search. Full text articles of relevant abstracts were reviewed, as were reference lists and citations.

Over the next year, the authors Z.I. and C.G.L. modified the Taragano criteria, the Mendonca FTD-MCI criteria, and the NIA-AA Alzheimer's Disease criteria to incorporate current nomenclature and research. These criteria were then presented to the NPS-PIA at AAIC 2013 in Boston, Massachusetts. The criteria were then modified via in an iterative process during presentations at four of the monthly NPS-PIA conference calls where expert members provided input leading to further modifications. For members unable to participate in conference calls, feedback was provided by e-mail and incorporated into the evolving criteria. It was decided by consensus to maintain the name MBI. It was felt there was much to be gained nosologically in keeping consistent with the MCI nomenclature, given the goal of trying to describe a spectrum of disease from cognitively normal through to dementia and including MCI. The "mild" in this case does not refer to symptom severity, but rather to the cognitive symptoms, which if present, would be of no greater severity than to warrant an MCI diagnosis. The manuscript describing the criteria was then written by Z.I. and C.G.L. and distributed to PIA workgroup chairs and coauthors for revisions and edits. The final version of this article was then distributed to NPS-PIA membership for approval and then subsequently to ISTAART for final approval before submission.

2.2. MBI criteria

The basis of these criteria is the assumption that neurodegeneration can manifest with personality change, as well as behavioral or other psychiatric symptoms in advance of cognitive impairment, depending on the type and location of pathology. MBI is intended to be an umbrella concept to describe a syndrome in which late-life onset of psychiatric symptoms that are not described in other nosologies (e.g., major depression, generalized anxiety, delusional disorder and so forth) are early manifestations of neurodegenerative

disease. Although the overall concept is broad, MBI has been broken down into the five domains of motivation, affective regulation, impulse control, social cognition, and perception/thought content. The proposed diagnostic criteria for MBI allow for, but do not require, the concurrent presence of MCI (Table 3). As MBI and MCI are both prodromes to dementia, NPSs after the onset of dementia are not considered to be MBI.

2.3. Summary of MBI criteria

The ISTAART MBI criteria (Table 3) expand on the description of behavioral changes dividing them into five subcategories of motivation, affect, impulse control, social appropriateness, and perception/thought content. The role of cognitive impairment has been more clearly defined as has the description of functional impairment due to behavioral rather than cognitive symptoms. Dementia remains an exclusion criterion; MCI can be present but is not required.

3. Diagnostic considerations

3.1. Function

The ISTAART MBI criteria require at least minimal functional impairment. Of importance, in MBI, the impairment in social, occupational, or interpersonal function must be attributable to NPS, such as changes in personality and behavior, and not to cognitive decline. When cognitive impairment causes “significant impairment in social or occupational functioning” then, the patient should be considered to have dementia, not MBI. If MBI is diagnosed concurrently with MCI, the functional impairment must be attributed to behavior or personality changes, and not the cognitive impairments, although this may be difficult to ascertain at times. The ISTAART NPS recommends the use of the NIA-AA consensus criteria for MCI and dementia. With regard to functional impairment in MCI, the NIA-AA criteria state that “Persons with MCI commonly have mild problems performing complex functional tasks which they used to perform previously, such as paying bills, preparing a meal, or shopping. They may take more time, be less efficient, and make more errors at performing such activities than in the past. Nevertheless, they generally maintain their independence of function in daily life, with minimal aids or assistance. It is recognized that the application of this criterion is challenging, as it requires knowledge about an individual’s level of function at the current phase of their life. However, it is noteworthy that this type of information is also necessary for the determination of whether a person is demented” [43]. Again, although this may be challenging, it is important to determine the cause of functional impairment (cognition vs. behavior) as it pertains to the diagnosis of MBI.

3.2. MBI versus subsyndromal or emerging psychiatric illness and developmental aspects of aging

Although a goal of the MBI criteria is to assess psychiatric symptomatology as a marker for incipient neurodegenerative illness, a potential confound is later life onset psychiatric disorders that may not be caused by neurodegeneration. These illnesses can include mood disorder, anxiety disorder, bereavement, psychotic disorder, and adjustment disorders. MBI criteria stipulate that “the behavioral changes are not attributable to another current

psychiatric disorder." Because MBI criteria also state that behaviors should "persist, at least intermittently for ≥6 months" the diagnosis of adjustment disorder, which requires symptoms for less than 6 months, is excluded [44]. However, the challenge lies in assessing the potential confound of subsyndromal psychiatric illness and the buildup of psychiatric symptoms before a formal episode. "Subsyndromal" depression is a risk factor for major depression, especially in older adults [45,46], and late life depression can be a risk factor for or prodrome of dementia [47]. The MBI criteria will include subsyndromal psychiatric disorders, some of which will evolve over 6 months and be excluded from MBI. However, some subsyndromal psychiatric disorders will continue to meet criteria for MBI, and the specificity of MBI criteria in this area is not known. Similarly, some individuals will exhibit persistent personality changes after the age of 50 years that are not related to psychiatric disorder or neurodegenerative disorder, but to developmental aspects of aging or adaptive changes in response to persistent change in social or environmental milieu. Further work and research evidence will help to refine this and inform improvements in the criteria.

3.3. Utility of proposed criteria

In extending the previous literature describing MBI and operationalizing the criteria, we have expanded criteria to include another possible preclinical phenotype. The proposed criteria will be subject to establishment of interrater and test-retest reliability, and validity for their ability to detect dementia early and for prognosticating late-onset NPS in the context of dementia. The criteria are proposed to stimulate further research into the nature of later-life onset NPS in the presence and absence of mild cognitive symptoms.

In addition to the early detection of neurodegenerative disease, the proposed MBI criteria may play a role in prevention. For example, in the Citalopram for Agitation in Alzheimer Disease trial, the effect of an antidepressant on agitation in nondepressed AD patients has been described [48,49]. Although effective for agitation and behavioral symptoms, citalopram was associated with slightly worsening cognition. The separation of behavioral and cognitive outcomes suggests the possibility of different or partially discrete neurobiological underpinnings for different symptoms that are core to the neurodegenerative process. Perhaps using treatments successful for NPS in dementia at the MBI stage could alter illness course. Certainly further research is required, and the proposed MBI criteria create a framework to test these hypotheses. Although it may be helpful to develop additional specific rating scales for MBI, existing instruments such as the Neuropsychiatric Inventory (NPI) [50] or its clinician rated version (NPI-C) [51] may be adequate. These instruments were developed primarily for use in dementia and may not fully capture the range or severity of NPS that occur in MBI. Nonetheless, the NPI is a valid and reliable means of measuring NPS in dementia and MCI and has been used in clinical trials and longitudinal studies [9,10,49,52]. MBI subcategories that may correlate with NPI domains include decreased motivation (NPI: apathy/ indifference); affective dysregulation (NPI: depression/ dysphoria, anxiety, elation/euphoria, and irritability); impulse dyscontrol (NPI: agitation/aggression, aberrant motor behavior, and appetite/eating behavior); social inappropriateness (NPI: disinhibition); abnormal perception/thought content (NPI: delusions and hallucinations).

4. Conclusions

We propose research diagnostic criteria for MBI as a potential way to detect earlier incipient neurodegenerative illness. The criteria extend previous research in this area and incorporate MCI into the framework. They will facilitate research into understanding NPS as a very early consequence of neurodegenerative disease in some cases, exploring targets for treatment and studying mechanisms of illness progression. The criteria will be subject to studies of reliability, concurrent validity, predictive validity, and the development of biomarkers, ultimately leading to therapeutics.

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RESEARCH IN CONTEXT

1. Systematic review: Pubmed and Medline searches were performed with search criteria “mild behavioral impairment,” “MBI,” “prodromal dementia,” “neuropsychiatric symptoms of dementia,” “non-cognitive symptoms of dementia,” “NPS,” “behavioral and psychological symptoms of dementia,” and “BPSD.” Both the American and United Kingdom spelling of “behavior/behaviour” were used in the search. Full text articles of relevant abstracts were reviewed, as were reference lists and citations to ensure a thorough search was performed.
2. Interpretation: Neuropsychiatric symptoms (NPS) can manifest early in the course of neurodegenerative illness. Currently, diagnosis of neurodegenerative disease is predicated on cognitive impairment. Based on the literature search and through an iterative process within the NPS Professional Interest Area of The International Society to Advance Alzheimer Research and Treatment, we propose research diagnostic criteria for mild behavioral impairment (MBI), as an extension of the preexisting MBI construct to include, but not mandate cognitive impairment. These are the first broadly reaching criteria to systematize and operationalize the MBI construct.
3. Future directions: The next steps in understanding the role of NPS in early manifestation of dementia include validating the MBI construct across different clinical domains. Both retrospective and prospective studies will be undertaken to determine the validity and reliability of MBI.

Table 1

Taragano MBI criteria

1.	Persistent behavioral changes and mild psychiatric symptoms, especially disinhibition
2.	No serious memory complaints
3.	Normal activities of daily living
4.	Not demented

Abbreviation: MBI, mild behavioral impairment.

Table 2

FT-MCI criteria (de Mendonca et al. [41])

1	Symptoms of frontotemporal dysfunction
	a. Behavioral symptoms, namely alterations in personal awareness, neglect of hygiene and grooming; alterations in social awareness, lack of social tact, misdemeanors; early signs of disinhibition, sexual changes, violence, jocularity, restless pacing; mental rigidity and inflexibility; hyperorality; stereotyped and perservative behaviour; utilization behaviour; distractibility, impulsivity, impersistence; and loss of insight
	b. Affective symptoms, namely depression, anxiety, sentimentality, suicidal and fixed ideation, delusion; hypochondriasis, bizarre somatic preoccupation; emotional unconcern, indifference, and remoteness, apathy, lack of empathy and sympathy; amimia, inertia, aspontaneity
	c. Speech disturbance, namely reduction of speech or stereotyped speech. These symptoms should be confirmed by an informant; the patient could also have memory complaints
2	Alteration (reduction of at least 1 SD) in at least one test reflecting executive functions dependent on the frontal lobe, namely attention (cancellation task), verbal initiative, motor initiative, graphomotor initiative, and conceptual thinking (verbal, interpretation of proverbs; or nonverbal, progressive matrices)
3	Maintained activities of daily living; the patient should both keep the professional, social, familial activities by clinical judgment and have a score in the part of the Blessed Dementia Scale concerning everyday activities and change in habits <3.
4	CT or MRI scan normal or with frontotemporal atrophy.

Abbreviations: FT-MCI, frontotemporal MCI; MCI, mild cognitive impairment; SD, standard deviation; CT, computed tomography; MRI, magnetic resonance imaging.

Table 3

ISTAART research diagnostic criteria for MBI

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 clear change from the person's usual behavior or personality as evidenced by at least one of the following:
	a. Decreased motivation (e.g., apathy, aspontaneity, indifference)
	b. Affective dysregulation (e.g., anxiety, dysphoria, changeability, euphoria, irritability)
	c. Impulse dyscontrol (e.g., agitation, disinhibition, gambling, obsessiveness, behavioral perseveration, stimulus bind)
	d. Social inappropriateness (e.g., lack of empathy, loss of insight, loss of social graces or tact, rigidity, exaggeration of previous personality traits)
	e. Abnormal perception or thought content (e.g., delusions, hallucinations)
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
	d. 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 (e.g., generalized anxiety disorder, major depression, manic or psychotic disorders), 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.

Abbreviations: ISTAART, International Society to Advance Alzheimer's Research and Treatment; MBI, mild behavioral impairment; MCI, mild cognitive impairment.