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RESEARCH ARTICLE

Diagnostic criteria for apathy in neurocognitive disorders

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Abstract

Introduction: Apathy is common in neurocognitive disorders (NCD) but NCD-specific diagnostic criteria are needed.

Methods: The International Society for CNS Clinical Trials Methodology Apathy Work Group convened an expert group and sought input from academia, health-care, industry, and regulatory bodies. A modified Delphi methodology was followed, and included an extensive literature review, two surveys, and two meetings at international conferences, culminating in a consensus meeting in 2019.

Results: The final criteria reached consensus with more than 80% agreement on all parts and included: limited to people with NCD; symptoms persistent or frequently recurrent over at least 4 weeks, a change from the patient's usual behavior, and including one of the following: diminished initiative, diminished interest, or diminished emotional expression/responsiveness; causing significant functional impairment and not exclusively explained by other etiologies.

Discussion: These criteria provide a framework for defining apathy as a unique clinical construct in NCD for diagnosis and further research.

KEYWORDS
apathy, behavior, cognition, diagnostic criteria, emotion, motivation, neurocognitive disorder (NCD), neuropsychiatric symptoms (NPS)

1 | BACKGROUND

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) term neurocognitive disorders (NCD) includes dementias (major NCD), such as Alzheimer's disease (AD), vascular dementia (VaD), frontotemporal lobar degeneration (FTD), dementia with Lewy bodies (DLB), and Parkinson's disease dementia (PDD), and mild NCD such as mild cognitive impairment (MCI). While NCD are characterized by a decline in one or more cognitive domains they are frequently accompanied by neuropsychiatric symptoms (NPS) such as apathy.[1] Apathy is broadly understood to refer to a lack of interest, enthusiasm, or concern (Oxford Dictionary).

Apathy symptoms are highly prevalent across NCD despite being defined a variety of ways.[2] In those with MCI, apathy symptoms have been detected in up to 51% of patients.[19] In vascular MCI (vMCI), apathy symptoms were reported in 17% to 88% of patients,[20] with higher prevalence in those with more severe cognitive impairment. In a meta-analysis of AD patients, apathy was the most common NPS, present in 49% of the pooled sample.[21] Apathy has been shown to increase with AD severity, with 19% of patients reporting symptoms in mild AD,[22] and 88% in moderate–severe AD.[23] In a multicenter clinical trial of mild-to-moderate VaD, 65% of patients exhibited apathy symptoms,[24] with the prevalence ranging from 53% in those with mild impairment to 92% in those with severe impairment.[25] Apathy symptoms are common in those with FTD,[26] occurring in approximately 57% of those with the language-variety FTD,[27] and up to 100% in moderate-to-severe FTD.[25,28] In DLB, apathy symptoms have been reported in 48% of patients with mild impairment[18] and up to 100% in patients with severe impairment.[25]

Apathy symptoms have also been consistently associated with negative consequences. They increase the likelihood of progression from normal cognition to MCI,[3] and from MCI to AD.[4,5] In those with amnestic MCI, the risk of progression to AD was almost seven-fold higher in those with apathy symptoms compared to those without.[6] Additionally, those with amnestic MCI and apathy symptoms had a faster progression to dementia compared to those without.[7] In AD, apathy symptoms have been linked with more rapid cognitive decline,[8] more impaired basic and instrumental activities of daily living,[9] and greater caregiver burden.[10] Apathy symptoms have also been associated with increased mortality in nursing home[11] and community-dwelling patients with AD.[12] In VaD, apathy symptoms have been correlated with poorer basic and instrumental activities of daily living.[13] In FTD, PD, and DLB, apathy symptoms were correlated with increased caregiver burden.[14–16] Apathy in DLB has been identified as a significant determinant of lower quality of life,[17] a predictor of faster cognitive decline, and shorter time until admission to nursing homes.[18]

1.1 | Problem statement

To date, apathy has commonly been defined using arbitrary cut-offs on various scales meant to capture symptom burden rather than with specific diagnostic criteria. Diagnostic criteria would provide a consistent definition of apathy, which in turn could advance research, particularly

that delineating the neurobiological correlates of apathy and identifying effective treatments for patients.

1.2 | Definitions of apathy

Originally described in 1991, Marin defined apathy as a disorder of motivation with cognitive, sensory, motor, and affective subtypes.[29] That definition was echoed by Cummings et al. in 1994 with the development of the Neuropsychiatric Inventory (NPI).[30] In 2000, Stuss et al. defined apathy as a disorder of initiative, manifesting in lack of self-initiated action, cause of which may be affective, behavioral, or cognitive in nature. That definition also included "social apathy," considered a disorder of sense of self and social awareness.[31] In 2002, through the development of the Apathy Inventory, Robert et al. conceptualized apathy as a disorder of motivation with emotional blunting, lack of initiative, and lack of interest.[32] In 2006, Sockeel et al. developed the Lille Apathy Rating Scale with the idea that apathy was a disorder of intellectual curiosity, action initiation, emotion, and self-awareness.[33] That same year, Levy and Dubois focused on apathy as a disorder of voluntary and goal-directed behaviors, with three theoretically envisaged subtypes of disrupted "signal" processing: emotional-affective, cognitive, and auto-activation.[34] Similarly, in 2008, Starkstein and Leentjens viewed apathy as a disorder of motivation with diminished goal-directed behavior and cognition.[35] While past efforts overlapped, inconsistencies between the definitions and scales used have resulted in the lack of a clear definition of clinically significant apathy.

1.3 | Previous diagnostic criteria

In 2008 the European Psychiatric Association (EPA) recognized the need for apathy diagnostic criteria specific to AD and other neurodegenerative diseases. The resulting criteria[36] required that apathy be diagnosed based on a loss of or diminished motivation and the presence of at least one symptom in at least two of three domains of apathy (reduced goal-directed behavior, goal-directed cognitive activity, or emotions). Those criteria also stated that the symptoms must result in clinically significant impairment and not be explained by other possible causes, such as physical disabilities, change in level of consciousness, or the effect of a substance. In addition, the EPA criteria delineated apathy as a persistent state, with symptoms pertaining to both self-initiated or "internal" actions as well as the patient's responsiveness to "external" stimuli. Since then, there have been considerable advances in apathy research.[2] In recognition of that, in 2018 an international consensus group used a rigorous transdiagnostic approach to update the 2009 EPA diagnostic criteria and expand their focus beyond NCD[38] while operationalizing the criteria and providing guidance on updated assessment tools. As a result, the term "motivation" was replaced by "goal-directed behavior/activity"; "domains" were re-labelled "dimensions"; the domains of behavior and initiative were combined; and a new dimension, social interaction, was introduced.

RESEARCH IN CONTEXT

1. **Systematic Review**: The authors reviewed the literature using traditional (e.g., PubMed) sources. As apathy has increasingly been recognized as a standalone construct in Alzheimer's disease and related neurocognitive disorders (NCD), there was a need to update the diagnostic criteria for apathy with a specific focus on NCD. The relevant references are appropriately cited.
2. **Interpretation**: The consensus process resulted in a set of diagnostic criteria for apathy in NCD that has had input from experts from academia, industry, and regulatory bodies.
3. **Future directions**: Future directions include the operationalization of these criteria, validation in both research and clinical settings, and development of new or validation of existing assessment scales.

HIGHLIGHTS

- International academia, industry and regulatory experts formed an Apathy Workgroup.
- Consensus criteria for apathy diagnosis in neurocognitive disorders were developed.
- Criteria form a framework for defining apathy for use in diagnosis and research.

However, those criteria focus more broadly on brain disorders rather than NCD.

1.4 | The need for apathy diagnostic criteria in NCD

The International Society for CNS Clinical Trials and Methodology (ISCTM) and the EPA appreciated the need for updated diagnostic criteria for apathy in NCD. These would incorporate the emerging understanding of the neurobiology and neurocircuitry of apathy in NCD, and recognize that memory problems, a core feature of NCD, make self-reporting unreliable as the disease progresses. Criteria also needed to be applicable to those living in long-term care facilities with variable self-sufficiency in activities of daily living, and potential limitations in access to activities and socialization. Therefore, existing criteria needed to be revised to incorporate the assessment of observable traits by an informant (clinician or caregiver). The need for revised criteria was also warranted due to potential confusion between apathy and other symptoms present in NCD, such as cognitive impairment, physical impairment, and depression. Finally, the growing interest in

TABLE 1 Consensus survey results

	Percentage of respondents that agreed with the statement
1. Do you agree with Criterion A: "The patient meets criteria for mild or major neurocognitive disorder (e.g.: AD, FTD, DLB, vascular dementia, a pre-dementia cognitive impairment syndrome such as mild cognitive impairment, prodromal AD, subjective cognitive impairment, or other cognitive disorder)"	85.9
2a. Do you agree that Criterion B1, formerly known as "behavior," should be labeled as "loss of initiative"?	85.7
2b. Do you agree that Criterion B2, formerly known as "cognition," should be labeled as "loss of interest"?	86.4
2c. Do you agree that Criterion B3, formerly known as "emotion," should be labeled as "emotional blunting"?	94.4
2d. Do you agree that Criterion B4, "loss of social activity," should be considered an independent domain?	59.4
3. Do you agree with Criterion C: "These symptoms cause clinically significant impairment in personal, social, occupational, and/or other important areas of functioning."	88.1
4. Do you agree with Criterion D: "These symptoms are not exclusively explained by physical disabilities, motor disabilities, diminished level of consciousness, or the direct physiological effects of a substance?	87.3
5. Do you feel that these criteria apply to all neurocognitive disorders? - Yes, definitely - Yes, somewhat - Yes, a little bit - No- Unsure	37.7 42.6 2.5 5.7 11.5
6. Do you feel that these criteria are useful for clinical purposes?	92.7
7. Do you feel that these criteria are useful for research purposes?	90.2

Abbreviations: AD, Alzheimer's disease; DLB, dementia with Lewy bodies; FTD, frontotemporal lobar degeneration.

apathy as a target for interventions further emphasized the need for diagnostic clarification. The current paper describes the collaborative, international consensus process led by the ISCTM Apathy Work Group (AWG) to update the diagnostic criteria for apathy specifically in NCD.

2 | METHODS: CONSENSUS-BUILDING PROCESS

The ISCTM-AWG consisted of experts from academia, industry, and regulatory bodies who recognized the need to better understand, identify, and manage apathy and to provide a basis for further apathy-related research. The 2018 Revised Diagnostic Criteria were used as an initial framework. As the purpose of this undertaking was not to develop diagnostic criteria de novo, a five-step modified Delphi methodology was followed: (1) literature review, (2) preliminary survey, (3) preliminary international meeting (to define criteria), (4) consensus survey, and (5) final international meeting (to finalize consensus criteria). The criteria were finalized in July 2019. Details of the consensus-building process can be found in the Appendix.

3 | RESULTS

Results of the first three steps, (1) literature review, (2) preliminary survey, and (3) details from the preliminary international meeting to define criteria, are included in the Appendix. In summary, the literature review supported keeping the cognitive and behavioral domains separate for NCD, and not introducing a social withdrawal domain. Results from the preliminary survey indicated strong agreement that diagnostic criteria specific for apathy in NCD are important for research and clinical practice. Any issues raised in the preliminary survey were discussed further at the subsequent preliminary international meeting.

3.1 | Consensus survey

The consensus survey had 143 respondents from 30 countries. Of those, 29% were members of ISCTM, 33% were members of the International Psychogeriatric Association (IPA), and 41% were members of the International Society to Advance Alzheimer's Research and Treatment (ISTAART) NPS Professional Interest Area (PIA) group, with some respondents being members of multiple groups. The majority of respondents were physicians (62%), with 11% of respondents from industry, and 4% of respondents from regulatory bodies. Survey results are summarized in Table 1.

3.2 | Final international meeting

Consensus on the wording of the apathy diagnostic criteria for NCD was reached at the final meeting (Table 2). The initial wording was revised in the following ways:

Criterion A (Primary diagnoses):

- Amended from "mild or major neurocognitive disorder" to "a syndrome of cognitive impairment or dementia" as defined by either International Classification of Diseases (ICD) or DSM-5 criteria. This

TABLE 2 Consensus diagnostic criteria for apathy in neurocognitive disorders

For a diagnosis of apathy, the patient needs to meet criteria A, B, C, and D		
Criterion A. Primary diagnoses	The patient meets criteria for a syndrome of cognitive impairment or dementia (as defined by either ICD or DSM-5 criteria; e.g.: AD, vascular dementia, FTD, DLB, PDD, a pre-dementia cognitive impairment syndrome such as MCI, prodromal AD, or other cognitive disorder).	
Criterion B. Symptoms and duration	The patient exhibits at least one symptom in at least two of the following three dimensions (B1 to B3). These symptoms have been persistent or frequently recurrent for a minimum of 4 weeks and represent a change from the patient's usual behavior. These changes may be reported by the patient themselves or by observation of others.	
	Dimension B1	Diminished initiative: Less spontaneous and/or active than usual self: Less likely to initiate usual activities such as hobbies, chores, self-care, conversation, work-related or social activities
	Dimension B2	Diminished interest: Less enthusiastic about usual activities: - Less interested in, or less curious about events in their environment - Less interested in activities and plans made by others - Less interested in friends and family - Reduced participation in activities even when stimulated - Less persistence in maintaining or completing tasks or activities
	Dimension B3	Diminished emotional expression/responsiveness: - Less spontaneous emotions - Less affectionate compared to their usual self - Expresses less emotion in response to positive or negative events - Less concerned about the impact of their actions on other people - Less empathy
Criterion C. Exclusionary criteria	These symptoms are not exclusively explained by psychiatric illnesses, intellectual disability, physical disabilities, motor disabilities, change in level of consciousness, or the direct physiological effects of a substance.	
Criterion D. Severity	These symptoms cause clinically significant impairment in personal, social, occupational, and/or other important areas of functioning. This impairment must be a change from their usual behaviour.	

Abbreviations: AD, Alzheimer's disease; DLB, dementia with Lewy bodies; DSM, Diagnostic and Statistical Manual of Mental Disorders; FTD, frontotemporal lobar degeneration; ICD, International Classification of Diseases; MCI, mild cognitive impairment; PDD, Parkinson's disease dementia.

was done as the group felt that the terms mild or major NCD were too specific to one discipline, and could cause confusion.

- Amended by removing subjective cognitive impairment (SCI), and including mild vascular cognitive impairment, as the group felt that SCI was outside the intended scope of these criteria.

Criterion B (Symptoms and duration):

- Amended to remove Domain B4 (Social Interaction) as it was felt that there was insufficient evidence to support it as a separate domain in patients with NCD at this time, and there was no consensus among survey respondents with regard to its inclusion. The examples of behaviors previously listed under B4 could also be encompassed by diminished interest, initiative, and emotional expression/responsiveness, and were therefore integrated into domains B1 (Diminished initiative), B2 (Diminished interest), and B3 (Diminished emotional expression/responsiveness). However, the workgroup agreed that should evidence arise in the future that demonstrates the need to separate social interactions, that decision would be reconsidered. The limited opportunity for social interaction in certain care settings or living situations of patients with NCD was also discussed.
- Amended so that each domain started with the word "diminished" as it was felt that this consistency would make the criteria easier to apply.
- Amended so that the term "domain" was replaced with "dimension," for consistency with the 2018 diagnostic criteria for apathy across brain diseases.
- Dimensions B1, B2, and B3 had more examples, as it was felt that the examples in the initial wording were not generalizable enough.
- Dimensions B1 and B2 were renamed from "behavior" and "cognition" to "initiative" and "interest," respectively.
- Dimension B3 was renamed, changing from "emotional blunting" to "diminished emotional expression/ responsiveness." It was suggested by the workgroup that "emotional blunting" did not encompass the full extent of the intended behavior, and that "diminished emotional expression/responsiveness" was most consistent with the intent of the dimension.

Criterion C (Exclusionary criteria)

- Amended to emphasize the exclusion of patients with psychiatric illnesses and changes in level of consciousness.

Criterion D (Severity)

- Amended to reiterate that these behaviors should constitute a change from the patient's usual behavior. The group felt that this was a potential point of confusion that required emphasis.

The order of Criterion C and Criterion D were reversed.

4 | DISCUSSION

The ISCTM-AWG expert panel collaborated extensively with relevant stakeholder groups to develop a set of consensus criteria for the diagnosis of apathy in NCD. The panel adopted a broad definition of the population under study by replacing the initial DSM-5–specific terminology of mild or major NCD, with a syndrome of cognitive impairment or dementia as defined by either ICD or DSM-5 criteria. For additional clarification, the final wording includes a list of sample disorders. SCI was excluded from this list as it was deemed to be outside the scope of these criteria. While a framework has been proposed for SCI,[114] the definition of SCI is evolving and uncertainty remains as to the best definition to predict future decline.[115] These criteria also excluded mild behavioral impairment (MBI) without cognitive impairment as that diagnosis was thought to be beyond the purview of these diagnostic criteria.[116] In addition, apathy symptoms are already part of MBI, as one of MBI domains is decreased motivation/drive.[116]

The dimensions "behavior" and cognition" were relabeled as "initiative" and "interest" due to confusion in the context of NCD. Specifically, as apathy in NCD is a behavior, there was confusion as to the meaning behind the "behavior" dimension. Additionally, since the criteria are specific to those with cognitive disorders, there was confusion as to whether the cognition dimension was an assessment of overall cognitive ability.

Social interaction was not included as an independent domain in the current diagnostic criteria, in contrast to the diagnostic criteria in brain disorders,[38] as there was insufficient evidence from the literature to support social interaction as a distinct and identifiable domain. Instead, social interactions are considered under *initiation* of social interactions (dimension B1) and *interest* in social interactions (dimension B2). Social interactions are complex and it is unclear which aspects should be considered in a diagnosis of apathy. One could argue that according to the Research Domain Criteria (RDoC), the social process domain would include affiliation and attachment and that affiliation is a behavioral consequence of social motivation.[117] However, it was felt that additional aspects of social interaction might be mediated by neurocircuitry that may or may not totally overlap with apathy in NCD.

Consistent with a basic diagnostic structure, these criteria specify that apathy must not be wholly explained by another current comorbid psychiatric, physical, or motor illness, or any change in level of consciousness or the direct physiological effects of a substance. This criterion, specific to patients with cognitive impairment or dementia, shares wording with the apathy diagnostic criteria across brain disorders.[38] A major area of discussion when developing these criteria was the overlap between apathy and other NPS, such as depression, and anhedonia as they can co-occur but are considered distinct.[118–121] Apathy is often difficult to distinguish from depression as both can have diminished interest, loss of pleasure in activities (anhedonia), and decreased energy.[120,122] As described above, the hallmark symptoms of apathy in NCD are diminished initiative, diminished interest, and diminished emotional expression/responsiveness. However, symptoms like sadness, hopelessness, guilt, tearfulness, and suicidal ideation (whether active or passive) are specific to depression and may not be present in those with apathy.[119] Furthermore, though anhedonia can co-occur with apathy and depression, it is not a requirement to have anhedonia to reach a diagnosis of apathy or depression.[43] For these reasons, we specified that apathy symptoms are not exclusively explained by psychiatric illnesses (e.g., depression) among other exclusions.

Another area of discussion was the potential misidentification of apathy as cognitive and/or physical impairment in patients with NCD. For example, patients may not be able to demonstrate initiative (domain B1) due to increased cognitive impairment, or because of long-standing low initiative. As such, wording of the criterion specified that the symptom must represent a change from the patient's usual behavior. Furthermore, as physical impairment increases with NCD severity, there was concern that patients may not have the opportunity to physically engage in their usual hobbies and activities. Consequently, a diagnosis of apathy could be missed, or a physical impairment could be misdiagnosed as apathy. For this reason, the wording of criterion B was carefully chosen to be applicable to those who may be wheelchair bound. It was also specified in criterion C that symptoms of apathy could not be explained by physical disabilities.

The final aspect of the diagnostic criteria is that apathy should be of a severity that causes significant impairment or disruption in functioning. Functional deficits are independently associated with apathy across NCD including AD,[8,123] MCI,[124,125] and dementia.[126] The presence of functional impairments may be observed in diverse contexts including personal, social, occupational, or other areas. This broad definition of deficits in daily functioning was selected to capture heterogeneity in the expression and scope of impairments related to diminished initiative, interest, and emotional expression/responsiveness. This criterion underlines the importance of identifying observable capacity across various functional areas. A specification to this criterion was added emphasizing that functional impairments must be a change from the typical level of functioning to qualify as supporting an apathy diagnosis. This distinction was specifically inserted to identify apathy related to NCD rather than apathy being a pre-existing behavioral or personality trait.

5 | CONCLUSIONS

Despite recognition of apathy symptoms and their impact, and an increased understanding of the underlying neurobiology of apathy,[73,75] there is a lack of currently available, effective treatments for these symptoms in dementia.[127,128] The ISCTM Working Group on Apathy

appreciated these issues and agreed that as a first step diagnostic clarification was needed.

It is important to recognize the limitations of diagnostic criteria for apathy, and any other NPS. NPS, such as apathy, occur in close conjunction with other neuropsychiatric and cognitive symptoms, and are therefore difficult to assess in isolation. Updated criteria may not address all issues regarding the identification, assessment, and treatment of apathy and this would be an oversimplification of the complexity of the apathy construct. Nevertheless, criteria will help consistently define a population of patients suffering from a clinically significant syndrome, even in the presence of differing underlying diseases.

Clinical trials of drugs targeting apathy are being pursued, and drug interventions based on knowledge of apathy neurocircuitry show promising results.[82,129] The stepwise process undertaken to create these diagnostic criteria for apathy involved multiple stakeholders, and benefited greatly by the involvement of individuals from the Food and Drug Administration (FDA) and European Medicines Agency (EMA). It is anticipated that applying a standard definition of apathy would ensure that all patients in clinical trials meet an agreed-upon definition of apathy, and that stakeholders will be given a portion of "the roadmap" necessary to facilitate development of treatments for apathy.

Future directions by the ISCTM-AWG include developing a scale that will address the three dimensions of apathy clearly, and detect clinically significant apathy in patients with NCD. This scale will include relevant examples and definitions to ensure the criteria are being applied appropriately. Validation of the consensus criteria is also a necessary next step to confirm its clinical and research utility. This will be achieved through future research using these criteria and comparing it to the diagnostic criteria across brain disorders. Findings from those studies will also provide valuable information relevant to clinical diagnosis, service provision, and apathy research, and will provide information on possible updates to the criteria to help users in the identification and treatment of apathy in NCD.

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CONFLICTS OF INTEREST

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APPENDIX

METHODS

Literature review

A literature review of the apathy in NCD populations was undertaken to answer two questions in NCD populations: whether evidence supported separating or combining cognitive and behavioral dimensions, and whether the literature supported social interaction as a separate domain in NCD. These questions were important to address the applicability of those aspects of the transdiagnostic apathy criteria by Robert et al.[32] to NCD.

Literature search terms were developed by team members to investigate the following areas: AD-related scales, non-AD–related scales, neuropathology/neurochemistry, neuroimaging, clinical trials, and neurocircuitry considerations using an RDoC framework. Common search

terms between these areas included Alzheimer's disease, mild cognitive impairment, vascular dementia, vascular cognitive impairment, frontotemporal dementia, Lewy bodies disease, Parkinson's disease dementia, neurocognitive disorders, and dementia. The Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta MEdica Database, PubMed, and PsycINFO databases were searched for original articles, systematic reviews, and meta-analyses related to each of the areas. These data were presented to the experts at the first international meeting to define criteria.

Preliminary Survey

The ISCTM-AWG created an online survey in 2018 to gather input from its members using the Robert et al.[32] 2018 Revised Apathy Diagnostic Criteria as a framework. Open-ended survey questions related to: the importance of having apathy diagnostic criteria in clinical and research practice, the targeted purpose of such diagnostic criteria, the importance of changing the terminology of "apathy," agreement with the questions associated with criteria, and suggestions as to how to revise existing criteria. In accordance with the Delphi method, participants completed the survey anonymously, which eliminated group pressures for conformity. In addition to the ISCTM-AWG, participants included stakeholders from the FDA and EMA to limit purposive sampling. Purposive sampling would lead to inclusion of participants interested in the diagnosis of apathy for clinical and research purposes, which may differ from those who decline participation.

Preliminary international meeting (to define criteria)

After the completion and analysis of the survey, the ISCTM-AWG met in July 2018 to discuss the literature review, and to assess the need for diagnostic criteria for apathy specific to NCD. Based on the discussion from this meeting, the chairs of the workgroup (KL, DM) drafted wording for the consensus diagnostic criteria.

Consensus survey

The ISCTM-AWG initial draft of the diagnostic criteria was then sent out as a survey to members of the ISCTM-AWG, the IPA, and the ISTAART NPS-PIA group. In addition, leaders of each of these stakeholder groups were invited to form a core multi-association working group. This survey asked for agreement on each item of the criteria, as well the relevance of these criteria to clinical and research practices. Participants were also able to provide additional comments regarding their agreement or disagreement for each of the survey questions. Similar to the preliminary survey, participants were anonymous and represented a broad group to reduce group conformity and purposive sampling, respectively.

Final international meeting (to finalize consensus criteria)

The ISCTM-AWG met in February 2019 to review preliminary results of the survey, to confirm the domains considered important to diagnostic criteria for apathy, and to revise the criteria wording based on feedback. In July 2019 a consensus meeting was held to finalize the wording of the diagnostic criteria. The discussion included representatives from the ISCTM-AWG, IPA, ISTAART NPS-PIA, and regulatory bodies. The wording of each criterion was discussed and a vote taken. The organizers of the ISCTM-AWG meeting then finalized the consensus diagnostic criteria that emerged from the meeting.

RESULTS

Literature review

The majority of AD-related (reviewed in Mohammad et al.[41]) and non-AD-related scales,[42–57] addressed three domains (behavioral, cognitive, and emotional) and focused on observable behaviors, which is appropriate for major NCD. However, studies using those scales did not provide evidence as to whether the cognitive and behavioral should be combined or kept separate. Because social interaction had not been separated in any definition of apathy prior to the recent update of the EPA diagnostic criteria,[38] only one study sought to find evidence for it as a separate domain.[43] In one single photon emission computed tomography scan and one pharmacological challenge study,[58] some evidence was found for the separation of the cognitive and behavioral domains, but the majority of studies have only examined apathy as a whole.[59–63] Neuroimaging studies suggest that affective apathy and cognitive apathy correlate with damage to different regions (striatal or orbitofrontal and dorsolateral prefrontal cortex, respectively).[64–81] Those studies also highlight that the neurocircuitry of apathy has similarities across NCD, despite different disease processes targeting different components of the circuit.[75] Of the 49 clinical trials reviewed (21 pharmacological,[82] 28 non-pharmacological trials[83–108]), none examined the apathy dimensions separately.

The RDoC framework necessarily breaks apathy into its components.[109] Apathy appears as a behavior under the sensorimotor domain (Construct: Motor Actions, Subconstruct: Initiation). However, studies have classified apathy as either a dysfunction of the arousal/modulation construct of the Arousal and Regulatory System, or under Positive Valence Systems.[110] It was concluded that there was value in keeping cognitive and behavioral domains separate for NCD based on neurobiological evidence, as well as clinical practicality because these domains can be separated through interview questions. Additionally, we reviewed the social withdrawal construct as proposed by Porcelli et al.,[111] which suggests some transdiagnostic commonality for AD, schizophrenia, and major depressive disorder on the "social brain." Despite the potential overlap between social withdrawal and apathy-related brain regions and neurocircuitry, the apathy construct appears differentiated from the social withdrawal construct.

Preliminary survey

The preliminary survey was sent to 39 individuals, of whom 28 (71.7%) responded. Response options were: "not important at all," "not very important," "important," "very important," and "extremely important." Of those, 46% were from academia, 32% from industry, and 22% were clinicians. It was universally agreed upon that it was important for research (100%) and clinical practice (96%). In terms of targets for clinical and research purposes, respondents almost unanimously agreed on the targets. Results are summarized in Table A1.

TABLE A1 Preliminary survey results

Question	% answering "important," "very important," or "extremely important"
For research purposes, how important are the diagnostic criteria for the following targets?	
- To improve understanding of the phenomenology	100.0
- To improve the understanding of the neuroanatomical and biological correlates	100.0
- To help clinicians in the choice of the pharmacologic treatments	96.4
- To improve the population selection criteria in pharmacological clinical trials	100.0
- To improve the population selection criteria in non-pharmacological clinical trials	92.9
For clinical purposes, how important are the diagnostic criteria for the following targets?	
- To improve prevention strategies	75.0
- To improve diagnostic and assessment strategies	100.0
- To help clinicians in the choice of pharmacologic treatments	96.4
- To help clinicians in the choice of non-pharmacologic treatments	92.9
- To help family caregivers to understand the pathology and put in place care strategies	85.7
- To help professional caregivers to understand the pathology and put in place care strategies	96.4

Preliminary international meeting (to define criteria)

This meeting covered issues raised by responses to the preliminary survey. Key questions raised were:

Should the terminology of "apathy" be changed?

Most attendees agreed to continue using the term "apathy," and to revise the definition, and ensure that the operationalization of the term is agreed upon.

Should the terminology of "emotion" (Dimension B3) be changed?

There was unanimous agreement at the meeting that the term "emotion" should be changed, as it may cover heterogeneous features, and may include mood symptoms that overlap with apathy. Alternative terms, such as "loss of emotional responsiveness," "emotional blunting," and "affect" were suggested.

What, if anything, distinguishes apathy from depression and anhedonia?

There was unanimous agreement that apathy and depression were different and distinct from one another. There was, however, some discussion as to how to distinguish apathy from anhedonia, or whether anhedonia was a subcomponent of apathy. Anhedonia is defined as the decrease in the ability to experience pleasure from previously enjoyable activities, and is a major symptom in depression and one of the negative symptoms in schizophrenia.[135] Anhedonia and apathy may both reflect syndromes of motivation, and may influence effort-based decision making for reward.[136] Despite this overlap, careful study has distinguished between the two and determined that anhedonia can be present in the absence of apathy. For NCD, the emphasis is on observable behaviors rather than symptoms that require patient insight.

Are there additional considerations to have apathy as an indication for treatment?

Participants at the meeting agreed that we need a clearer idea of the neurocircuitry and neurobiology of apathy as a distinct entity within the pathophysiology of dementia, and whether there are differences from other diagnostic groups, such as schizophrenia.

Assessment of apathy: caregiver, patient, and/or clinician?

There was general agreement that while all three groups are important, in this population, given the lack of/diminished insight of patients, that caregiver and clinician reports should be given greater weight.

After these discussions, the initial revised criteria were drafted by the organizers of the meeting.