


RESEARCH ARTICLE

# Diagnostic criteria for apathy in neurocognitive disorders

David S. Miller<sup>1,#</sup> | Philippe Robert<sup>2,3,4,#</sup> | Larry Ereshefsky<sup>5</sup> | Lawrence Adler<sup>6</sup> |  
Daniel Bateman<sup>7</sup> | Jeff Cummings<sup>8,9</sup> | Steven T. DeKosky<sup>10</sup> | Corinne E. Fischer<sup>11,12</sup> |  
Masud Husain<sup>13,14,15</sup> | Zahinoor Ismail<sup>16</sup> | Judith Jaeger<sup>17</sup> | Alan J. Lerner<sup>18</sup> |  
Abby Li<sup>19</sup> | Constantine G. Lyketsos<sup>20</sup> | Valeria Manera<sup>2,3</sup> | Jacobo Mintzer<sup>21</sup> |  
Hans J. Moebius<sup>22</sup> | Moyra Mortby<sup>23</sup> | Didier Meulien<sup>24</sup> | Stephane Pollentier<sup>25</sup> |  
Anton Porsteinsson<sup>26</sup> | Jill Rasmussen<sup>27</sup> | Paul B. Rosenberg<sup>20</sup> |  
Myuri T. Ruthirakuhan<sup>19</sup> | Mary Sano<sup>28</sup> | Carla Zuccheri Sarracini<sup>19</sup> |  
Krista L. Lanctôt<sup>19,29,#</sup> 

<sup>1</sup> Signant Health, Blue Bell, Pennsylvania, USA

<sup>2</sup> Cognition Behaviour Technology Lab, Université Côte d'Azur, Nice, France

<sup>3</sup> Association Innovation Alzheimer, Nice, France

<sup>4</sup> Centre Memoire, Centre Hospitalier Universitaire de Nice, Nice, France

<sup>5</sup> Follow the Molecule, Marina del Rey, California, USA

<sup>6</sup> Department of Psychiatry, University of Maryland School of Medicine, Baltimore, Maryland, USA

<sup>7</sup> Department of Psychiatry, Indiana University School of Medicine, Indianapolis, Indiana, USA

<sup>8</sup> Department of Brain Health, School of Integrated Health Sciences, University of Nevada, Las Vegas, Nevada, USA

<sup>9</sup> Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, Nevada, USA

<sup>10</sup> Department of Neurology, McKnight Brain Institute University of Florida, Gainesville, Florida, USA

<sup>11</sup> Institute of Medical Science University of Toronto, Toronto, Ontario, Canada

<sup>12</sup> Keenan Research Centre for Biomedical Research, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada

<sup>13</sup> Department of Experimental Psychology, University of Oxford, Oxford, UK

<sup>14</sup> Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK

<sup>15</sup> Oxford NIHR Biomedical Research Centre, Oxford, UK

<sup>16</sup> Hotchkiss Brain Institute University of Calgary, Calgary, Alberta, Canada

<sup>17</sup> CognitionMetrics, Wilmington, Delaware, USA

<sup>18</sup> University Hospitals - Case Western Reserve University, Cleveland, Ohio, USA

<sup>19</sup> Sunnybrook Research Institute, Toronto, Ontario, Canada

<sup>20</sup> Johns Hopkins University, Baltimore, Maryland, USA

<sup>21</sup> Medical University of South Carolina and Ralph H. Johnson Veterans Administration Medical Center, Charleston, South Carolina, USA

<sup>22</sup> Moebius-Consult, Baar, Switzerland

<sup>23</sup> UNSW Ageing Futures Institute The University of New South Wales, Sydney, Australia

<sup>24</sup> Clinical Research and Development, H. Lundbeck A/S, Valby, Denmark

<sup>25</sup> Boehringer Ingelheim Pharma GmbH & Co KG, CNS Diseases Research, Biberach an der Riss, Germany

<sup>26</sup> University of Rochester, Rochester, New York, USA

<sup>27</sup> Psi-Napse, Dorking, UK

<sup>28</sup> Alzheimer Disease Research Center, Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York, USA

<sup>29</sup> Departments of Psychiatry and Pharmacology/Toxicology, University of Toronto, Toronto, Ontario, Canada

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2021 The Authors. *Alzheimer's & Dementia* published by Wiley Periodicals LLC on behalf of Alzheimer's Association

**Correspondence**

Krista L. Lancôt, Neuropsychopharmacology Research Group, Sunnybrook Health Sciences Centre, 2075 Bayview Ave, FG52, Toronto, ON, Canada, M4N 3M5.  
E-mail: [krista.lancot@sunnybrook.ca](mailto:krista.lancot@sunnybrook.ca)

#David S. Miller, Philippe Robert, and Krista L. Lancôt are equal contributors to first-authorship.

**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.<sup>1</sup> 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.<sup>2</sup> In those with MCI, apathy symptoms have been detected in up to 51% of patients.<sup>19</sup> In vascular MCI (vMCI), apathy symptoms were reported in 17% to 88% of patients,<sup>20</sup> 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.<sup>21</sup> Apathy has been shown to increase with AD severity, with 19% of patients reporting symptoms in mild AD,<sup>22</sup> and 88% in moderate-severe AD.<sup>23</sup> In a multicenter clinical trial of mild-to-moderate VaD, 65% of patients exhibited apathy symptoms,<sup>24</sup> with the prevalence ranging from 53% in those with mild impairment to 92% in those with severe impairment.<sup>25</sup> Apathy symptoms are common in those with FTD,<sup>26</sup> occurring in approximately 57% of those with the language-variety FTD,<sup>27</sup> and up to 100% in moderate-to-severe FTD.<sup>25,28</sup> In DLB, apathy symptoms have been reported in 48% of

patients with mild impairment<sup>18</sup> and up to 100% in patients with severe impairment.<sup>25</sup>

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

**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.<sup>29</sup> That definition was echoed by Cummings et al. in 1994 with the development of the Neuropsychiatric Inventory (NPI).<sup>30</sup> 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.<sup>31</sup> 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.<sup>32</sup> 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.<sup>33</sup> 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.<sup>34</sup> Similarly, in 2008, Starkstein and Leentjens viewed apathy as a disorder of motivation with diminished goal-directed behavior and cognition.<sup>35</sup> 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<sup>36</sup> 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.<sup>2</sup> 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<sup>38</sup> 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?	37.7
- Yes, definitely	42.6
- Yes, somewhat	2.5
- Yes, a little bit	5.7
- No- Unsure	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		
<b>Criterion A.</b> 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).	
<b>Criterion B.</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
<b>Criterion C.</b> 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.	
<b>Criterion D.</b> 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,<sup>114</sup> the definition of SCI is evolving and uncertainty remains as to the best definition to predict future decline.<sup>115</sup> 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.<sup>116</sup> In addition, apathy symptoms are already part of MBI, as one of MBI domains is decreased motivation/drive.<sup>116</sup>

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,<sup>38</sup> 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.<sup>117</sup> 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.<sup>38</sup> 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.<sup>118-121</sup> Apathy is often difficult to distinguish from depression as both can have diminished interest, loss of pleasure in activities (anhedonia), and decreased energy.<sup>120,122</sup> 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.<sup>119</sup> 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.<sup>43</sup> 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 longstanding 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,<sup>8,123</sup> MCI,<sup>124,125</sup> and dementia.<sup>126</sup> 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,<sup>73,75</sup> there is a lack of currently available, effective treatments for these symptoms in dementia.<sup>127,128</sup> 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.<sup>82,129</sup> 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.

## ACKNOWLEDGMENTS

The authors would like to thank the following individuals for their contributions to the process of developing these diagnostic criteria: Tiffany Farchione (FDA), Jean Kim (FDA), Nancy Dickinson (FDA), Javier Muniz (FDA), Mike Davis (FDA), Valentina Mantua (formerly EMA, now FDA), Bruce Cuthbert (NIMH), and Jovier Evans (NIMH). This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## CONFLICTS OF INTEREST

Dr. Miller is a full-time employee of Signant Health. Dr. Robert reports grants from French Alzheimer's Association, French research ministry ANR, European H20 20 programs, French National Solidarity council, University Côte d'azur Idex; and consulting fees from Lundbeck and Servier outside the submitted work. Dr. Ereshefsky receives support from APEX Innovative Services, which conducts research for most pharma, and performing site for NIDA, and through Follow the Molecule LLC receives consulting compensation from Biogen,

BioXcel, Neurocrine, Taisho, Atlas Investments, Athira, Intracellular, Cerevel, and Karuna. Dr. Adler has no relevant disclosures. Dr. Bate-man reports no conflicts of interest or disclosures. Dr. Cummings has provided consultation to Acadia, Actinogen, AgeneBio, Alkahest, Alzheon, Annovis, Avanir, Axsome, Biogen, BioXcel, Cassava, Cerecin, Cerevel, Cortexyme, EIP Pharma, Eisai, Foresight, GemVax, Genentech, Green Valley, Grifols, Karuna, Merck, Novo Nordisk, Otsuka, Resverlogix, Roche, Samumed, Samus, Signant Health, Suven, Third Rock, and United Neuroscience pharmaceutical and assessment companies. Dr. Cummings has stock options in ADAMAS, AnnovisBio, MedAvante, and BiOasis. Dr. Cummings owns the copyright of the Neuropsychiatric Inventory. Dr. Cummings is supported by Keep Memory Alive (KMA), NIGMS grant P20GM109025, NINDS grant U01NS093334, and NIA grant R01AG053798. Dr. DeKosky chairs the medical advisory boards for Acumen and Cognition Therapeutics the DSMB for Biogen, is the editor for *Up To Date*, and is the Associate Editor for *Neurotherapeutics*. Dr. Fischer receives grant funding from Brain Canada, Patient Centred Outcomes Research Trust-Fund, St. Michaels Hospital Foundation, Hoffman LaRoche, and Vielight Inc, all outside the submitted work. Dr. Husain reports grants from the Wellcome Trust, NIHR Biomedical Research Centre Oxford, European Union; and consulting fees from Otsuka, outside the submitted work. Dr. Ismail has received research support from the Alzheimer Society of Calgary, Brain Canada, Canadian Consortium on Neurodegeneration in Aging, Canadian Institutes of Health Research, and consulting fees from Janssen, Lundbeck, and Otsuka, all outside the submitted work. Dr. Jaeger is the owner of CognitionMetrics, LLC, which over the past two years has held consulting contracts with Acadia, Aptinix, Biogen, Eisai, Harmony, INmune Bio, Iproteos, Ironwood, Jazz Pharma, Janssen, LuMind, Lundbeck, Otsuka, Ovid, Perception, and Syndesi. Dr. Lerner receives grant support from National Institute on Aging, ADDF, Global Alzheimer's Platform foundation, and the Elizabeth Severance Prentiss Foundation. Ms. Li reports no conflicts of interest. Dr. Lyketsos has received grant funding from NIMH, NIA, Associated Jewish Federation of Baltimore, Weinberg Foundation, Forest, Glaxo-Smith-Kline, Eisai, Pfizer, Astra-Zeneca, Lilly, Ortho-McNeil, Bristol-Myers, Novartis, National Football League, Elan, Functional Neuromodulation, Bright Focus Foundation; has been a consultant or advisor to Astra-Zeneca, Glaxo-Smith Kline, Eisai, Novartis, Forest, Supernus, Adlyfe, Takeda, Wyeth, Lundbeck, Merz, Lilly, Pfizer, Genentech, Elan, NFL Players Association, NFL Benefits Office, Avanir, Zinfandel, BMS, AbbVie, Janssen, Orion, Otsuka, Servier, Astellas, Roche, Karuna, SVB Leerink, Maplight, Axsome; and has received honoraria or travel support from Pfizer, Forest, Glaxo-Smith Kline, and Health Monitor. Dr. Manera has no conflicts of interests to disclose. Dr. Mintzer has received research support from the National Institute on Aging, Alzheimer's Disease Cooperative Study (ADCS), Alzheimer's Disease Trials Research Institute (ATRI), Alzheimer's Clinical Trials Consortium (ACTC), Eisai Pharmaceuticals, AgeneBio, TauRx, ACADIA, Novartis, and Biogen as well as consulting fees from Otsuka, ACADIA, and Avanir. Dr. Moebius receives consulting compensation from Exciva and Athira through moebius-consult LLC, all outside the submitted work. Dr. Mortby is supported by the Australian National Health

and Medical Research Council (NHMRC) and Australian Research Council (ARC) Dementia Research Development Fellowship (#1102028). Dr. Muelien is a full-time employee of H. Lundbeck SAS. Dr. Pollentier is a full-time employee of Boehringer Ingelheim International GmbH. Dr. Porsteinsson reports personal fees from Acadia Pharmaceuticals, Avanir, Cadent Therapeutics, Functional Neuromodulation, Syneos, and BioXcel; and grants to his institution from Avanir, Biogen, Biohaven, Eisai, Eli Lilly, Genentech/Roche, and Novartis. Dr. Rasmussen is an independent consultant to psi-napse, is an advisor to the NHS (Academic Health Science Network Kent, Surrey, Sussex, Surrey Heartlands ICS), and receives funding for consultancy/advisory board/speaker's bureau from Acadia, Alz Soc, Andera Partners, Biogen, ConSynance, Merck, Nuricia, and Roche. Dr. Rosenberg has received research support from the National Institute on Aging, Alzheimer's Association, Lilly, Functional Neuromodulation (FNMI), Lilly, Alzheimer's Disease Cooperative Study (ADCS), Alzheimer's Disease Trials Research Institute (ATRI), Alzheimer's Clinical Trials Consortium (ACTC), as well as consulting fees from GLG, Leerink, Otsuka, Avanir, ITI, IQVIA, Food and Drug Administration, Cerevel, Bioxcel, and Sunovion, all outside the submitted work. Dr. Ruthirakuhan has received funding through a Canadian Institute of Health Research postdoctoral fellowship. Dr. Sano reports no conflicts of interest. Ms. Zuccheri Sarracini report no conflicts of interest. Dr. Lanctôt reports grants from Alzheimer's Association, Alzheimer Society of Canada, Alzheimer's Drug Discovery Foundation, Canadian Institutes of Health Research, National Institute on Aging; and consulting fees from Abide, BioXcel, Cerevel, Exciva, Highmark Interactive, ICG Pharma, Kondor Pharma, and Otsuka, outside the submitted work.

## ORCID

Krista L. Lanctôt  <https://orcid.org/0000-0001-7024-6637>

## REFERENCES

- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.): American Psychiatric Association Publishing; 2013.
- Lanctôt KL, Aguera-Ortiz L, Brodaty H, et al. Apathy associated with neurocognitive disorders: recent progress and future directions. *Alzheimers Dement*. 2017;13:84-100.
- Geda YE, Roberts RO, Mielke MM, et al. Baseline neuropsychiatric symptoms and the risk of incident mild cognitive impairment: a population-based study. *Am J Psychiatry*. 2014;171:572-581.
- Richard E, Schmand B, Eikelenboom P, et al. Symptoms of apathy are associated with progression from mild cognitive impairment to Alzheimer's disease in non-depressed subjects. *Dement Geriatr Cogn Disord*. 2012;33:204-209.
- Ruthirakuhan M, Herrmann N, Vieira D, Gallagher D, Lanctôt KL. The roles of apathy and depression in predicting Alzheimer disease: a longitudinal analysis in older adults with mild cognitive impairment. *Am J Geriatr Psychiatry*. 2019;27:873-882.
- Palmer K, Di Iulio F, Varsi AE, et al. Neuropsychiatric predictors of progression from amnesic-mild cognitive impairment to Alzheimer's disease: the role of depression and apathy. *J Alzheimers Dis*. 2010;20:175-183.
- Somme J, Fernandez-Martinez M, Molano A, Zarranz JJ. Neuropsychiatric symptoms in amnesic mild cognitive impairment: increased risk and faster progression to dementia. *Curr Alzheimer Res*. 2013;10:86-94.
- Starkstein SE, Jorge R, Mizrahi R, Robinson RG. A prospective longitudinal study of apathy in Alzheimer's disease. *J Neurol Neurosurg Psychiatry*. 2006;77:8-11.
- Onyike CU, Sheppard JM, Tschanz JT, et al. Epidemiology of apathy in older adults: the Cache County Study. *Am J Geriatr Psychiatry*. 2007;15:365-375.
- Dauphinaut V, Delphin-Combe F, Mouchoux C, et al. Risk factors of caregiver burden among patients with Alzheimer's disease or related disorders: a cross-sectional study. *J Alzheimers Dis*. 2015;44:907-916.
- Nijsten JMH, Leontjevas R, Pat-El R, Smalbrugge M, Koopmans R, Gerritsen DL. Apathy: risk factor for mortality in nursing home patients. *J Am Geriatr Soc*. 2017;65:2182-2189.
- Vilalta-Franch J, Calvo-Perxas L, Garre-Olmo J, Turro-Garriga O, Lopez-Pousa S. Apathy syndrome in Alzheimer's disease epidemiology: prevalence, incidence, persistence, and risk and mortality factors. *J Alzheimers Dis*. 2013;33:535-543.
- Zawacki TM, Grace J, Paul R, et al. Behavioral problems as predictors of functional abilities of vascular dementia patients. *J Neuropsychiatry Clin Neurosci*. 2002;14:296-302.
- Bjoerke-Bertheussen J, Ehrh U, Rongve A, Ballard C, Aarsland D. Neuropsychiatric symptoms in mild dementia with lewy bodies and Alzheimer's disease. *Dement Geriatr Cogn Disord*. 2012;34:1-6.
- Massimo L, Powers C, Moore P, et al. Neuroanatomy of apathy and disinhibition in frontotemporal lobar degeneration. *Dement Geriatr Cogn Disord*. 2009;27:96-104.
- Merrilees J, Dowling GA, Hubbard E, Mastick J, Ketelle R, Miller BL. Characterization of apathy in persons with frontotemporal dementia and the impact on family caregivers. *Alzheimer Dis Assoc Disord*. 2013;27:62-67.
- Bostrom F, Jonsson L, Minthon L, Londos E. Patients with dementia with lewy bodies have more impaired quality of life than patients with Alzheimer disease. *Alzheimer Dis Assoc Disord*. 2007;21:150-154.
- Breitve MH, Bronnick K, Chwiszczuk LJ, Hynninen MJ, Aarsland D, Rongve A. Apathy is associated with faster global cognitive decline and early nursing home admission in dementia with Lewy bodies. *Alzheimers Res Ther*. 2018;10:83.
- Sherman C, Liu CS, Herrmann N, Lanctôt KL. Prevalence, neurobiology, and treatments for apathy in prodromal dementia. *Int Psychogeriatr*. 2018;30:177-184.
- Nakamura K, Kasai M, Ouchi Y, et al. Apathy is more severe in vascular than amnesic mild cognitive impairment in a community: the Kurihara Project. *Psychiatry Clin Neurosci*. 2013;67:517-525.
- Zhao QF, Tan L, Wang HF, et al. The prevalence of neuropsychiatric symptoms in Alzheimer's disease: systematic review and meta-analysis. *J Affect Disord*. 2016;190:264-271.
- Treiber KA, Lyketsos CG, Corcoran C, et al. Vascular factors and risk for neuropsychiatric symptoms in Alzheimer's disease: the Cache County Study. *Int Psychogeriatr*. 2008;20:538-553.
- Hart DJ, Craig D, Compton SA, et al. A retrospective study of the behavioural and psychological symptoms of mid and late phase Alzheimer's disease. *Int J Geriatr Psychiatry*. 2003;18:7-1042.
- Staekenborg SS, Koedam EL, Henneman WJ, et al. Progression of mild cognitive impairment to dementia: contribution of cerebrovascular disease compared with medial temporal lobe atrophy. *Stroke*. 2009;40:1269-1274.
- Kazui H, Yoshiyama K, Kanemoto H, et al. Differences of Behavioral and Psychological Symptoms of Dementia in Disease Severity in Four Major Dementias. *PLoS One*. 2016;11:e0161092.
- Mendez MF, Lauterbach EC, Sampson SM, Research ACo. An evidence-based review of the psychopathology of frontotemporal dementia: a report of the ANPA Committee on Research. *J Neuropsychiatry Clin Neurosci*. 2008;20:130-149.



27. Chow TW, Miller BL, Boone K, Mishkin F, Cummings JL. Frontotemporal dementia classification and neuropsychiatry. *Neurologist*. 2002;8:263-269.
28. Diehl-Schmid J, Pohl C, Perneczky R, Forstl H, Kurz A. Behavioral disturbances in the course of frontotemporal dementia. *Dement Geriatr Cogn Disord*. 2006;22:352-357.
29. Marin RS. Differential diagnosis and classification of apathy. *Am J Psychiatry*. 1990;147:22-30.
30. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology*. 1994;44:2308-2314.
31. Stuss DT, Van Reekum R, Murphy KJ. Differentiation of states and causes of apathy. In: Borod JC, ed. *Series in Affective Science The Neuropsychology of Emotion*. London, UK: Oxford University Press; 2000.
32. Robert PH, Clairet S, Benoit M, et al. The apathy inventory: assessment of apathy and awareness in Alzheimer's disease, Parkinson's disease and mild cognitive impairment. *Int J Geriatr Psychiatry*. 2002;17:1099-1105.
33. Sockeel P, Dujardin K, Devos D, Deneve C, Destee A, Defebvre L. The Lille apathy rating scale (LARS), a new instrument for detecting and quantifying apathy: validation in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2006;77:579-584.
34. Levy R, Dubois B. Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. *Cereb Cortex*. 2006;16:916-928.
35. Starkstein SE, Leentjens AF. The nosological position of apathy in clinical practice. *J Neurol Neurosurg Psychiatry*. 2008;79:1088-1092.
36. Robert P, Onyike CU, Leentjens AF, et al. Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders. *Eur Psychiatry*. 2009;24:98-104.
37. European Medical Association. European Medicines Agency workshop on the clinical investigation of medicines for the treatment of Alzheimer's disease 2014.
38. Robert P, Lanctot KL, Aguera-Ortiz L, et al. Is it time to revise the diagnostic criteria for apathy in brain disorders? The 2018 international consensus group. *Eur Psychiatry*. 2018;54:71-76.
39. Nobis L, Husain M. Apathy in Alzheimer's disease. *Curr Opin Behav Sci*. 2018;22:7-13.
40. Sultzer DL. Why apathy in Alzheimer's matters. *Am J Psychiatry*. 2018;175:99-100.
41. Mohammad D, Ellis C, Rau A, et al. Psychometric properties of apathy scales in dementia: a systematic review. *J Alzheimers Dis*. 2018;66:1065-1082.
42. Ahearn DJ, McDonald K, Barraclough M, Leroi I. An exploration of apathy and impulsivity in Parkinson disease. *Curr Gerontol Geriatr Res*. 2012;2012:390701.
43. Ang YS, Lockwood P, Apps MA, Muhammed K, Husain M. Distinct subtypes of apathy revealed by the apathy motivation index. *PLoS One*. 2017;12:e0169938.
44. Burns A, Folstein S, Brandt J, Folstein M. Clinical assessment of irritability, aggression, and apathy in Huntington and Alzheimer disease. *J Nerv Ment Dis*. 1990;178:20-26.
45. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord*. 2008;23:2129-2170.
46. Kay DB, Kirsch-Darrow L, Zahodne LB, Okun MS, Bowers D. Dimensions of apathy in Parkinson's disease: exploratory factor analysis of the apathy scale. *J Parkinsons Dis*. 2012;2:161-166.
47. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13:261-276.
48. Lyne J, Renwick L, Grant T, et al. Scale for the assessment of negative symptoms structure in first episode psychosis. *Psychiatry Res*. 2013;210:1191-1197.
49. Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the Apathy Evaluation Scale. *Psychiatry Res*. 1991;38:143-162.
50. Martinez-Martin P, Gil-Nagel A, Gracia LM, Gomez JB, Martinez-Sarries J, Bermejo F. Unified Parkinson's Disease Rating Scale characteristics and structure. The Cooperative Multicentric Group. *Mov Disord*. 1994;9:76-83.
51. Overall JE, Gorham DR. The brief psychiatric rating scale. *Psychological Reports*. 1962;10:799-812.
52. Pedersen KF, Alves G, Larsen JP, Tysnes OB, Moller SG, Bronnick K. Psychometric properties of the Starkstein Apathy Scale in patients with early untreated Parkinson disease. *Am J Geriatr Psychiatry*. 2012;20:142-148.
53. Raimo S, Trojano L, Spitaleri D, Petretta V, Grossi D, Santangelo G. Apathy in multiple sclerosis: a validation study of the apathy evaluation scale. *J Neurol Sci*. 2014;347:295-300.
54. Santangelo G, Barone P, Cuoco S, et al. Apathy in untreated, de novo patients with Parkinson's disease: validation study of Apathy Evaluation Scale. *J Neurol*. 2014;261:2319-2328.
55. Starkstein SE, Mayberg HS, Preziosi TJ, Andrezejewski P, Leiguarda R, Robinson RG. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. *J Neuropsychiatry Clin Neurosci*. 1992;4:134-139.
56. Starkstein SE, Merello M. The Unified Parkinson's Disease Rating Scale: validation study of the mentation, behavior, and mood section. *Mov Disord*. 2007;22:2156-2161.
57. Yazbek H, Norton J, Capdevielle D, et al. The Lille Apathy Rating Scale (LARS): exploring its psychometric properties in schizophrenia. *Schizophr Res*. 2014;157:278-284.
58. Herrmann N, Rothenburg LS, Black SE, et al. Methylphenidate for the treatment of apathy in Alzheimer disease: prediction of response using dextroamphetamine challenge. *J Clin Psychopharmacol*. 2008;28:296-301.
59. Lanctot KL, Herrmann N, Black SE, et al. Apathy associated with Alzheimer disease: use of dextroamphetamine challenge. *Am J Geriatr Psychiatry*. 2008;16:551-557.
60. Lanctot KL, Herrmann N, Rothenburg L, Eryavec G. Behavioral correlates of GABAergic disruption in Alzheimer's disease. *Int Psychogeriatr*. 2007;19:151-158.
61. Marshall GA, Donovan NJ, Lorusi N, et al. Apathy is associated with increased amyloid burden in mild cognitive impairment. *J Neuropsychiatry Clin Neurosci*. 2013;25:302-307.
62. Mori T, Shimada H, Shinotoh H, et al. Apathy correlates with prefrontal amyloid beta deposition in Alzheimer's disease. *J Neurol Neurosurg Psychiatry*. 2014;85:449-455.
63. Proitsi P, Lupton MK, Reeves SJ, et al. Association of serotonin and dopamine gene pathways with behavioral subphenotypes in dementia. *Neurobiol Aging*. 2012;33:791-803.
64. Aguera-Ortiz L, Hernandez-Tamames JA, Martinez-Martin P, et al. Structural correlates of apathy in Alzheimer's disease: a multimodal MRI study. *Int J Geriatr Psychiatry*. 2017;32:922-930.
65. Benoit M, Clairet S, Koulibaly PM, Darcourt J, Robert PH. Brain perfusion correlates of the apathy inventory dimensions of Alzheimer's disease. *Int J Geriatr Psychiatry*. 2004;19:864-869.
66. Fernandez-Matarrubia M, Matias-Guiu JA, Cabrera-Martin MN, et al. Different apathy clinical profile and neural correlates in behavioral variant frontotemporal dementia and Alzheimer's disease. *Int J Geriatr Psychiatry*. 2018;33:141-150.
67. Hollocks MJ, Lawrence AJ, Brookes RL, et al. Differential relationships between apathy and depression with white matter microstructural changes and functional outcomes. *Brain*. 2015;138:3803-3815.
68. Huey ED, Lee S, Cheran G, Grafman J, Devanand DP. Alzheimer's Disease Neuroimaging I. Brain Regions Involved in Arousal and Reward Processing are Associated with Apathy in Alzheimer's Disease and Frontotemporal Dementia. *J Alzheimers Dis*. 2017;55:551-558.

69. Joo SH, Lee CU, Lim HK. Apathy and intrinsic functional connectivity networks in amnesic mild cognitive impairment. *Neuropsychiatr Dis Treat.* 2017;13:61-67.
70. Kim HJ, Kang SJ, Kim C, et al. The effects of small vessel disease and amyloid burden on neuropsychiatric symptoms: a study among patients with subcortical vascular cognitive impairments. *Neurobiol Aging.* 2013;34:1913-1920.
71. Kitamura S, Shimada H, Niwa F, et al. Tau-induced focal neurotoxicity and network disruption related to apathy in Alzheimer's disease. *J Neurol Neurosurg Psychiatry.* 2018;89:1208-1214.
72. Kos C, van Tol MJ, Marsman JB, Knegtering H, Aleman A. Neural correlates of apathy in patients with neurodegenerative disorders, acquired brain injury, and psychiatric disorders. *Neurosci Biobehav Rev.* 2016;69:381-401.
73. Kumfor F, Zhen A, Hodges JR, Piguet O, Irish M. Apathy in Alzheimer's disease and frontotemporal dementia: distinct clinical profiles and neural correlates. *Cortex.* 2018;350-359.
74. Lansdall CJ, Coyle-Gilchrist ITS, Jones PS, et al. White matter change with apathy and impulsivity in frontotemporal lobar degeneration syndromes. *Neurology.* 2018;90:e1066-e76.
75. Le Heron C, Apps MAJ, Husain M. The anatomy of apathy: a neurocognitive framework for amotivated behaviour. *Neuropsychologia.* 2017.
76. Liseicka-Ford DM, Tozer DJ, Morris RG, Lawrence AJ, Barrick TR, Markus HS. Involvement of the reward network is associated with apathy in cerebral small vessel disease. *J Affect Disord.* 2018;232:116-121.
77. Migneco O, Benoit M, Koulibaly PM, et al. Perfusion brain SPECT and statistical parametric mapping analysis indicate that apathy is a cingulate syndrome: a study in Alzheimer's disease and nondemented patients. *Neuroimage.* 2001;13:896-902.
78. Ota M, Sato N, Nakata Y, Arima K, Uno M. Relationship between apathy and diffusion tensor imaging metrics of the brain in Alzheimer's disease. *Int J Geriatr Psychiatry.* 2012;27:722-726.
79. Starkstein SE, Brockman S. The neuroimaging basis of apathy: empirical findings and conceptual challenges. *Neuropsychologia.* 2018.
80. Theleritis C, Politis A, Siarkos K, Lyketsos CG. A review of neuroimaging findings of apathy in Alzheimer's disease. *Int Psychogeriatr.* 2014;26:195-207.
81. Zhao H, Tang W, Xu X, Zhao Z, Huang L. Functional magnetic resonance imaging study of apathy in Alzheimer's disease. *J Neuropsychiatry Clin Neurosci.* 2014;26:134-141.
82. Ruthirakuhan MT, Herrmann N, Abraham EH, Chan S, Lancot KL. Pharmacological interventions for apathy in Alzheimer's disease. *Cochrane Database Syst Rev.* 2018;5:CD012197.
83. Amieva H, Robert PH, Grandoulier AS, et al. Group and individual cognitive therapies in Alzheimer's disease: the ETNA3 randomized trial. *Int Psychogeriatr.* 2016;28:707-717.
84. Berg A, Sadowski K, Beyrodt M, et al. Snoezelen, structured reminiscence therapy and 10-minutes activation in long term care residents with dementia (WISDE): study protocol of a cluster randomized controlled trial. *BMC Geriatr.* 2010;10:5.
85. Chapman SB, Weiner MF, Rackley A, Hynan LS, Zientz J. Effects of cognitive-communication stimulation for Alzheimer's disease patients treated with donepezil. *J Speech Lang Hear Res.* 2004;47:1149-1163.
86. Di Domenico A, Palumbo R, Fairfield B, Mammarella N. Fighting apathy in Alzheimer's dementia: a brief emotional-based intervention. *Psychiatry Res.* 2016;242:331-335.
87. Ferrero-Arias J, Goni-Imizcoz M, Gonzalez-Bernal J, Lara-Ortega F, da Silva-Gonzalez A, Diez-Lopez M. The efficacy of nonpharmacological treatment for dementia-related apathy. *Alzheimer Dis Assoc Disord.* 2011;25:213-219.
88. Hattori H, Hattori C, Hokao C, Mizushima K, Mase T. Controlled study on the cognitive and psychological effect of coloring and drawing in mild Alzheimer's disease patients. *Geriatr Gerontol Int.* 2011;11:431-437.
89. Hokkanen L, Rantala L, Remes AM, Harkonen B, Viramo P, Winblad I. Dance/Movement Therapeutic methods in management of dementia. *J Am Geriatr Soc.* 2003;51:576-577.
90. Ikemata S, Momose Y. Effects of a progressive muscle relaxation intervention on dementia symptoms, activities of daily living, and immune function in group home residents with dementia in Japan. *Jpn J Nurs Sci.* 2017;14:135-145.
91. Lam LC, Lui VW, Luk DN, et al. Effectiveness of an individualized functional training program on affective disturbances and functional skills in mild and moderate dementia—a randomized control trial. *Int J Geriatr Psychiatry.* 2010;25:133-141.
92. Leone E, Deudon A, Bauchet M, et al. Management of apathy in nursing homes using a teaching program for care staff: the STIM-EHPAD study. *Int J Geriatr Psychiatry.* 2013;28:383-392.
93. Leontjevas R, Teerenstra S, Smalbrugge M, et al. More insight into the concept of apathy: a multidisciplinary depression management program has different effects on depressive symptoms and apathy in nursing homes. *Int Psychogeriatr.* 2013;25:1941-1952.
94. Nguyen JP, Boutoleau-Bretonniere C, Lefaucheur JP, et al. Efficacy of transcranial direct current stimulation combined with cognitive training in the treatment of Apathy in patients with Alzheimer's disease: study protocol for a randomized trial. *Rev Recent Clin Trials.* 2018;13:319-327.
95. Nguyen JP, Suarez A, Kemoun G, et al. Repetitive transcranial magnetic stimulation combined with cognitive training for the treatment of Alzheimer's disease. *Neurophysiol Clin.* 2017;47:47-53.
96. Niu YX, Tan JP, Guan JQ, Zhang ZQ, Wang LN. Cognitive stimulation therapy in the treatment of neuropsychiatric symptoms in Alzheimer's disease: a randomized controlled trial. *Clin Rehabil.* 2010;24:1102-1111.
97. Politis AM, Vozzella S, Mayer LS, Onyike CU, Baker AS, Lyketsos CG. A randomized, controlled, clinical trial of activity therapy for apathy in patients with dementia residing in long-term care. *Int J Geriatr Psychiatry.* 2004;19:1087-1094.
98. Raglio A, Bellelli G, Traficante D, et al. Efficacy of music therapy treatment based on cycles of sessions: a randomised controlled trial. *Aging Ment Health.* 2010;14:900-904.
99. Raglio A, Bellelli G, Traficante D, et al. Efficacy of music therapy in the treatment of behavioral and psychiatric symptoms of dementia. *Alzheimer Dis Assoc Disord.* 2008;22:158-162.
100. Rajkumar AP, Ballard C, Fossey J, et al. Apathy and its response to antipsychotic review and nonpharmacological interventions in people with Dementia living in nursing homes: wHELD, a factorial cluster randomized controlled trial. *J Am Med Dir Assoc.* 2016;17:741-747.
101. Sanchez A, Marante-Moar MP, Sarabia C, et al. Multisensory stimulation as an intervention strategy for elderly patients with severe Dementia: a pilot randomized controlled trial. *Am J Alzheimers Dis Other Demen.* 2016;31:341-350.
102. Staal JA, Sacks A, Matheis R, et al. The effects of Snoezelen (multisensory behavior therapy) and psychiatric care on agitation, apathy, and activities of daily living in dementia patients on a short term geriatric psychiatric inpatient unit. *Int J Psychiatry Med.* 2007;37:357-370.
103. Steinberg M, Leoutsakos JM, Podewils LJ, Lyketsos CG. Evaluation of a home-based exercise program in the treatment of Alzheimer's disease: the Maximizing Independence in Dementia (MIND) study. *Int J Geriatr Psychiatry.* 2009;24:680-685.
104. Tappen RM, Williams CL. Therapeutic conversation to improve mood in nursing home residents with Alzheimer's disease. *Res Gerontol Nurs.* 2009;2:267-275.
105. Telenius EW, Engedal K, Bergland A. Effect of a high-intensity exercise program on physical function and mental health in nursing home

- residents with dementia: an assessor blinded randomized controlled trial. *PLoS One*. 2015;10:e0126102.
106. Treusch Y, Majic T, Page J, Gutzmann H, Heinz A, Rapp MA. Apathy in nursing home residents with dementia: results from a cluster-randomized controlled trial. *Eur Psychiatry*. 2015;30:251-257.
  107. Valenti Soler M, Aguera-Ortiz L, Olazaran Rodriguez J, et al. Social robots in advanced dementia. *Front Aging Neurosci*. 2015;7:133.
  108. van Weert JC, van Dulmen AM, Spreeuwenberg PM, Ribbe MW, Bensing JM. Behavioral and mood effects of snoezelen integrated into . *J Am Geriatr Soc*. 2005;53:24.
  109. Insel T, Cuthbert B, Garvey M, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry*. 2010;167:748-751.
  110. Thant T, Yager J. Updating Apathy: using research domain criteria to inform clinical assessment and diagnosis of disorders of motivation. *J Nerv Ment Dis*. 2019;207:707-714.
  111. Porcelli S, Van Der Wee N, van der Werff S, et al. Social brain, social dysfunction and social withdrawal. *Neurosci Biobehav Rev*. 2019;97:10-33.
  112. Winsky-Sommerer R, de Oliveira P, Loomis S, Wafford K, Dijk DJ, Gilmour G. Disturbances of sleep quality, timing and structure and their relationship with other neuropsychiatric symptoms in Alzheimer's disease and schizophrenia: insights from studies in patient populations and animal models. *Neurosci Biobehav Rev*. 2019;97:112-137.
  113. Husain M, Roiser JP. Neuroscience of apathy and anhedonia: a transdiagnostic approach. *Nat Rev Neurosci*. 2018;19:470-484.
  114. Jessen F, Amariglio RE, van Boxtel M, et al. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimers Dement*. 2014;10:844-852.
  115. Rabin LA, Smart CM, Amariglio RE. Subjective cognitive decline in preclinical Alzheimer's disease. *Annu Rev Clin Psychol*. 2017;13:369-396.
  116. Ismail Z, Aguera-Ortiz L, Brodaty H, et al. The mild behavioral impairment checklist (MBI-C): a rating scale for Neuropsychiatric symptoms in Pre-Dementia populations. *J Alzheimers Dis*. 2017;56:929-938.
  117. National Institute of Mental Health. Development and definitions of the RDoC domains and constructs.
  118. Levy ML, Cummings JL, Fairbanks LA, et al. Apathy is not depression. *J Neuropsychiatry Clin Neurosci*. 1998;10:314-319.
  119. Mortby ME, Maercker A, Forstmeier S. Apathy: a separate syndrome from depression in dementia? A critical review. *Aging Clin Exp Res*. 2012;24:305-316.
  120. Starkstein SE, Ingram L, Garau ML, Mizrahi R. On the overlap between apathy and depression in dementia. *J Neurol Neurosurg Psychiatry*. 2005;76:1070-1074.
  121. Tagariello P, Girardi P, Amore M. Depression and apathy in dementia: same syndrome or different constructs? A critical review. *Arch Gerontol Geriatr*. 2009;49:246-249.
  122. Marin RS, Firinciogullari S, Biedrzycki RC. The sources of convergence between measures of apathy and depression. *J Affect Disord*. 1993;28:117-124.
  123. Benoit M, Andrieu S, Lechowski L, et al. Apathy and depression in Alzheimer's disease are associated with functional deficit and psychotropic prescription. *Int J Geriatr Psychiatry*. 2008;23:409-414.
  124. Rog LA, Park LQ, Harvey DJ, Huang CJ, Mackin S, Farias ST. The independent contributions of cognitive impairment and neuropsychiatric symptoms to everyday function in older adults. *Clin Neuropsychol*. 2014;28:215-236.
  125. Wadsworth LP, Lorus N, Donovan NJ, et al. Neuropsychiatric symptoms and global functional impairment along the Alzheimer's continuum. *Dement Geriatr Cogn Disord*. 2012;34:96-111.
  126. Bouwens SF, van Heugten CM, Aalten P, et al. Relationship between measures of dementia severity and observation of daily life functioning as measured with the Assessment of Motor and Process Skills (AMPS). *Dement Geriatr Cogn Disord*. 2008;25:81-87.
  127. Manera V, Abrahams S, Aguera-Ortiz L, et al. Recommendations for the Nonpharmacological Treatment of Apathy in Brain Disorders. *Am J Geriatr Psychiatry*. 2020;28:410-420.
  128. Theleritis C, Siarkos K, Katirtzoglou E, Politis A. Pharmacological and Nonpharmacological treatment for Apathy in Alzheimer disease: a systematic review across modalities. *J Geriatr Psychiatry Neurol*. 2017;30:26-49.
  129. Rosenberg PB, Lancot KL, Drye LT, et al. Safety and efficacy of methylphenidate for apathy in Alzheimer's disease: a randomized, placebo-controlled trial. *J Clin Psychiatry*. 2013;74:810-816.
  130. Burns A, Folstein S, Brandt J, Folstein M. Clinical assessment of irritability, aggression, and apathy in Huntington and Alzheimer disease. *J Nerv Ment Dis*. 1990;178:20-26.
  131. Lyne J, Renwick L, Grant T, et al. Scale for the assessment of negative symptoms structure in first episode psychosis. *Psychiatry Res*. 2013;210:1191-1197.
  132. Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the Apathy Evaluation Scale. *Psychiatry Res*. 1991;38:143-162.
  133. Lisiecka-Ford DM, Tozer DJ, Morris RG, Lawrence AJ, Barrick TR, Markus HS. Involvement of the reward network is associated with apathy in cerebral small vessel disease. *J Affect Disord*. 2018;232:116-121.
  134. Steinberg M, Leoutsakos JM, Podewils LJ, Lyketsos CG. Evaluation of a home-based exercise program in the treatment of Alzheimer's disease: the Maximizing Independence in Dementia (MIND) study. *Int J Geriatr Psychiatry*. 2009;24:680-685.
  135. Winsky-Sommerer R, de Oliveira P, Loomis S, Wafford K, Dijk DJ, Gilmour G. Disturbances of sleep quality, timing and structure and their relationship with other neuropsychiatric symptoms in Alzheimer's disease and schizophrenia: insights from studies in patient populations and animal models. *Neurosci Biobehav Rev*. 2019;97:112-137.
  136. Husain M, Roiser JP. Neuroscience of apathy and anhedonia: a transdiagnostic approach. *Nat Rev Neurosci*. 2018;19:470-484.

**How to cite this article:** Miller DS, Robert P, Ereshefsky L, et al. Diagnostic criteria for apathy in neurocognitive disorders. *Alzheimer's Dement*. 2021;1-13.  
<https://doi.org/10.1002/alz.12358>

## 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.<sup>32</sup> 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.<sup>32</sup> 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.<sup>41</sup>) and non-AD-related scales,<sup>42-57</sup> 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,<sup>38</sup> only one study sought to find evidence for it as a separate domain.<sup>43</sup> In one single photon emission computed tomography scan and one pharmacological challenge study,<sup>58</sup> 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.<sup>59-63</sup> Neuroimaging studies suggest that affective apathy and cognitive apathy correlate with damage to different regions (striatal or orbitofrontal and dorsolateral prefrontal cortex, respectively).<sup>64-81</sup> Those studies also highlight that the neurocircuitry of apathy has similarities across NCD, despite different disease processes targeting different components of the circuit.<sup>75</sup> Of the 49 clinical trials reviewed (21 pharmacological,<sup>82</sup> 28 non-pharmacological trials<sup>83-108</sup>), none examined the apathy dimensions separately.

The RDoC framework necessarily breaks apathy into its components.<sup>109</sup> 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.<sup>110</sup> 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.,<sup>111</sup> 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.<sup>135</sup> Anhedonia and apathy may both reflect syndromes of motivation, and may influence effort-based decision making for reward.<sup>136</sup> 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.