ISCTM Apathy Working Group Session

February 20, 2018
Washington, DC

Apathy Working Group Co-chairs:
Drs Krista Lanctôt and David Miller
Attendees

Larry Adler
Joanne Bell
Will Carpenter
John Davis
Aldermar Degroot
Nancy Dickinson
Larry Ereshefsky
Jovier Evans
Rebecca Evans
Tiffany Farchione
Udi Ghitza

Judy Jaeger
Jean Kim
Krista Lanctôt
Valentina Mantua
Didier Muelien
David Miller
Hans Moebius
Javier Muniz
Cedric O’Gorman
Luca Pani

Stephane Pollentier
Bill Potter
Jill Rasmussen
Myuri Ruthirakuhan
Sigurd Suessmuth
Juliette Toure
Daniel Umbricht
Dawn Velligan
Jim Yuakim
Silvia Zaragoza Domingo
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<td>David Miller</td>
<td>Introduction and overview</td>
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<td>Larry Ereshefsky</td>
<td>ISCTM viewpoint</td>
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<td>8:40 – 8:45</td>
<td>Tiffany Farchione</td>
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<td>Myuri Ruthirakahan</td>
<td>Results of preliminary survey</td>
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<td>Krista Lanctôt</td>
<td>Issues identified and process</td>
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<td>Overview of key questions</td>
<td>to be discussed in small groups</td>
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<td>9:00 – 10:00</td>
<td>Small Group Sessions</td>
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<td>Break</td>
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<td>10:15 – 11:15</td>
<td>Small group leader</td>
<td>presentations and Discussion</td>
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<td>D Miller/K Lanctôt</td>
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Selected slides from
Apathy: Diagnosis and Current Definitions, ADMET2 and Other Considerations in Clinical Trial Design, and Research Domain Criteria

FDA Mini-Symposium, February 8, 2018
Larry Ereshefsky, PharmD, BCPP, FCCP

Chief Scientific Officer, Early Phase, Hassman Research Institute
CSO and Owner, Follow the Molecule: CNS LLC

Retired Regents Professor of Pharmacy, Pharmacology and Psychiatry,
The University of Texas Health Science Center, San Antonio

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Krista Lanctot and David Miller, co-chairs, BPSD Apathy ISCTM
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Krista, David, Paul, Joanne Bell, ISTAART NPS, PIA Leadership (others)
Philippe Robert, European Psychiatry Association, Innovation Alzheimer’s Institute, Chair of Diagnosis Taskforce in EU

Disclosures:
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M3 Bio, Neuralstem, and Taisho R & D
Principal consultant, investigator, ProScience Research Group
**Research Domain Criteria 2.0**

**RDoC Framework: “Biomarker” & Target Discovery**

- **Trans-Diagnostic Platform**
  - *trans-level* target discovery
  - *across development*
Neurological disease models made clear

“Disease models inform our understanding of central nervous system disorder pathogenesis and enable testing of novel therapeutics. A frank discussion of the rationale for using particular preclinical disease models, as well as their limitations, may enable comparisons between studies and facilitate drug development.”

As a research framework, the RDoC initiative has called for a shift toward studying disease with a focus on basic dimensions of mental function that cut across current diagnostic boundaries. From this perspective, investigations into cellular, circuit and behavioral endophenotypes of a single model may lead to a better understanding of the pathophysiology of multiple disorders.”

• Parkinson’s, ALS-frontotemporal dementia, Alzheimer’s
• “… we would also encourage investigators to discuss their findings within the framework of the NIMH’s Research Domain Criteria initiative…” (21, 2015)
• NIAAA (alcoholism): “AA-RDoC” (focus on outcome measures for clinical trials) (Litten, … & Koob, Alcoholism: Clin & Exp Res, 2015)
In general, our “take” on neurological disorders would be that these are very heterogeneous disorders/syndromes, so can benefit from an approach that looks at effects in specific functional domains rather than treating the disorder as though it should have near-identical effects and symptoms across patients.”

Bruce Cuthbert Director RDoC NIMH, February 6. 2018 (email to LE)
Shift from categorical model i.e., infectious disease to a Complex Trait Model (full distribution).

Empirically-based cutpoints for (e.g.) mild, moderate, severe levels of dysfunction.

Level of Functioning

"Disease" vs. "Healthy"
And so we are faced with a paradox:

We can’t move past these neuroscientifically uninformative heterogeneous categorical diagnoses until we have a body of knowledge organized along neuroscientific principles.

RDoC was initiated to address this paradox

RDoC focuses on the primary neural circuits and functions that the brain has evolved to function adaptively,

To characterize the range of intact to disordered functioning,

And develop a classification scheme based on what we know about how the brain and behavior are organized.

- Regulatory agencies initial rejection of claim as “pseudo-specific” might be considered a “straw man” position
  - Objection may be overcome with arguments and data to show validity and value of targeting a particular domain or biomarker-defined subgroup
Apathy Diagnostic criteria: **reaffirm applicable to many patient populations**

For a diagnosis of apathy the patient should fulfil criteria A, B, C and D

A. **Core feature of apathy, diminished motivation**, present \( \geq 4 \) weeks

B. **2/3 dimensions of apathy, reduced goal-directed**:

- ✓ behavior
- ✓ cognitive activity
- ✓ Emotions
- ✓ Possibly add Social?

C. **Demonstrate significant impairment**

[functional, social impairment]

D. **Criteria exclude symptoms & states that mimic apathy**

- Inter-rater reliability high (kappa 0.93, \( p = 0.001 \))

Diagnostic criteria task force included members of the European Psychiatric Association, the European Alzheimer’s Disease Consortium and experts from Europe, Australia, and North America.

- **Potentially important mechanistic/regulatory Question:**

- Do each of the sub-domains: Behavior, Cognition, Emotion, and possibly the addition of Social add validity or heterogeneity to the research population?

- …need 2 of 3 in current Diagnostic Criteria

- Do each of the domains map to the same neurochemistry and circuitry?
“Biotypes: (1) Cognitive Control, (2) Sensorimotor Reactivity

- Schizophrenia
- Schizoaffective Disorder
- Psychotic Bipolar Disorder

Computational Psychopathology

- (1): Study specific brain or behavioral functions (e.g., membrane currents versus neural firing)
- (2): Examine specific neural/behavioral mechanisms (decision-making, reinforcement learning)
- (3): Computational approaches to diagnosis and biomarkers

Uma Vaidyanathan: RDoC Workgroup meeting
National Institute of Mental Health, 6 October 2017

Clementz, …. & Tamminga, Am J Psychiatry, in press
Human deep phenotyping of social withdrawal

Social Cognition tasks
Reward Processing tasks
Measure of sociability and social exploration

The project leading to this application has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115916. This Joint Undertaking receives support from the European Union’s Horizon 2020 research and innovation programme and EFPIA.
"Craddock and Owen published a comprehensive schematic that has several important parallels to RDoC – dimensional view of psychopathology, multiple units of analysis.

If we want to get to this, actually being able to identify these neural modules, biological systems, and genes, we need to change the way we’re asking questions."

RDoC Workgroup meeting, National Institute of Mental Health
6 October 2017
Apathy consistently associated with the dorsal anterior cingulate cortex, and the ventral striatum

Other regions implicated: insula, DLPFC and OFC

Selective vulnerability of different regions associated with variable disease process

Regional atrophy in reward regions – similar regions involved across diagnosis

If a drug treats apathy, it does not imply it treats atrophy

If you have atrophy with apathy in AD, but the same behavior occurs in other disorders with a different mechanism of deficit in the same brain region, then doesn’t this bolster the utility of apathy as a construct for drug treatment? (i.e., apathy in Parkinson’s and negative symptoms in Schizophrenia)

Does it make sense to ‘lump or split’?

Does the transdiagnostic presence of apathy, associated with similar brain region ‘malfunctions’ subsequently treated by a drug linked to the neurocircuitry and neuropharmacology of the region support the treatment target?
Further studies of the relationships between behavioral and/or neural signals obtained using these tasks and anhedonic pathology across diagnostic groups of psychiatric, neurologic and addictive disorders are needed in order to determine whether the observed relationships are robust measures of reward circuitry disturbances independent of disorder.

Many of the existing studies on anhedonia-related tasks and measures have been conducted using cross-sectional designs. It will be important to determine, via longitudinal research, the extent to which these tasks are able to reliably detect change in clinical pathology.

Ultimately, the clinical relevance and meaningfulness of changes in these paradigms will drive regulatory acceptance, be it for diagnostic or treatment evaluation purposes.

In more advanced AD these recommended tasks would not be possible to be reliably performed.

Use of MCI or Mild Behavioral Impairment (MBI) to validate circuitry in Amyloid/Tau positive patients could bridge AD to other disorders with reward path/motivation deficits (Ismail et al., 2016)

IF clinical gains were observed across AD spectrum, would early neurocircuitry/reward pathways study demonstrating beneficial drug effects be supportive of a claim spanning v mild - severe stages of illness?
**NPI-C: APATHY/INDIFFERENCE**

- Embedded in the NPI-C is the original NPI. Original NPI items are shaded.
- Unlike the NPI, the NPI-C allows the rater to obtain additional caregiver and patient information to inform the rating for each item.

**The patient interview is meant to provide you with an opportunity to interact with the patient thereby gaining information that you should use to inform the clinician rating.** It is not always practical or possible to interview the patient, or the patient may not be able to provide appropriate responses.

The clinician rating is a severity rating based on all available clinical (e.g., medical records, personal observations, personal experience and training) and interview information. The clinician rating of severity may differ from the caregiver rating if warranted.

**Is the NPI-C potentially an attractive strategy for use of the NPI across a wider range of illness severities?**

In MBI (Mild Behavioral Impairment) and eMCI, patient interview remains critical, and the caregiver is more of a ‘partner/companion’

With disease progression from eMCI to AD, reliance on the Care Giver report increases

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<table>
<thead>
<tr>
<th>Description</th>
<th>Caregiver Interview</th>
<th>Patient Interview</th>
<th>Clinical Impression</th>
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<tbody>
<tr>
<td>1. Does (S) seem less spontaneous and active than usual?</td>
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<tr>
<td>2. Is (S) less likely to initiate a conversation?</td>
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<td>3. Is (S) less affectionate or lacking in emotions when compared to his/her usual self?</td>
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<td>4. Does (S) contribute less to household chores?</td>
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<tr>
<td>5. Does (S) seem less spontaneous and active than usual?</td>
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<tr>
<td>6. Does (S) seem less interested in the activities and plans of others?</td>
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<td>7. Has (S) lost interest in friends and family members?</td>
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<tr>
<td>8. Is (S) less enthusiastic about his/her usual interests?</td>
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<td>9. Does (S) sit quietly without paying attention to things going on around him/her?</td>
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If you are also completing the original NPI, please ask the informant to provide the following global domain ratings for shaded items only:
- Frequency (0-4):  
- Severity (0-3):  
- Caregiver Distress (0-5):  
- Frequency x Severity:  

10. Has (S) reduced participation in social activities even when stimulated?  
11. Is (S) less interested in or curious about routine or new events in his/her environment?  
12. Does (S) express less emotion in response to positive or negative or events?  

Column Totals:  

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Preliminary ISCTM Apathy Work Group Survey Results

Presenter: Myuri Ruthirakkuhan
PhD Student
Sunnybrook Research Institute
Toronto, ON
RESULTS OF PRELIMINARY SURVEY

• Number of responses: 28

Which profession best describes you?

- 46.4% Academic
- 32.1% Academic
- 21.4% Industry

1 member from NIH
3 members from FDA
Areas of Agreement – *Importance in Clinic & Research*

How important is it to have apathy diagnostic criteria for the following?

Dr. Robert’s survey (Europe): ✔ Agreement
Areas of Disagreement – Terminology

Is it important to change the terminology of 'apathy'?

28 responses

Dr. Robert’s survey (Europe): ✓ Most agree to keep terminology as ‘apathy’

(10 yes: 6 no)
Areas of Disagreement – Terminology (cont.)

Dr. Robert’s survey (Europe): Motivation ‘deficit’ favoured over ‘disorder’. However, their members mention that keeping ‘apathy’ as ‘motivation’ disorders/deficit may include anhedonia, abolition, abulia
Other Areas of Agreement/Disagreement

• Current Diagnostic Criteria (Robert et al. 2010)

  – Criterion B1: **TERM:** Cognition
    **Defn:** “Loss of, or diminished *goal-directed activity* as evidenced by at least one of the following” (*cognitive* taken out of definition)

  – Criterion B2: **TERM:** Behaviour
    **Defn:** “Loss of, or diminished *goal-directed behaviour* as evidenced by at least one of the following” (same as previous)

  – Criterion B3: **TERM:** Emotion
    **Defn:** “Loss of, or diminished emotion as evidence by at least one of the following” (same as previous)
<table>
<thead>
<tr>
<th>Criterion B1 (Currently: Cognition)</th>
<th>Definition</th>
<th>Questions to operationalize</th>
<th>Change in terminology</th>
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<tbody>
<tr>
<td></td>
<td>Agreement: 75%</td>
<td>Self: 64 – 90%</td>
<td>“Lack of Interest”: 71%</td>
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<td></td>
<td></td>
<td>Environment: 93%</td>
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<tr>
<th>Criterion B2 (Currently: Behaviour)</th>
<th>Definition</th>
<th>Questions to operationalize</th>
<th>Change in terminology</th>
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<tr>
<td></td>
<td>Agreement: 93%</td>
<td>Self: 71 – 93%</td>
<td>“Lack of Initiative”: 89%</td>
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<td></td>
<td></td>
<td>Environment: 96%</td>
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<tr>
<th>Criterion B3 (Currently: Emotion)</th>
<th>Definition</th>
<th>Questions to operationalize</th>
<th>Change in terminology</th>
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<tr>
<td></td>
<td>Agreement: 82%</td>
<td>Self: 82%</td>
<td>No change (keep as emotion) 61%</td>
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<td></td>
<td></td>
<td>Environment: 89%</td>
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<tr>
<th>Dr. Robert’s Survey (Europe)</th>
<th>Definition</th>
<th>Questions to operationalize</th>
<th>Change in terminology</th>
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<tbody>
<tr>
<td>Agreement</td>
<td>Agreement</td>
<td>Agreement/ Disagreement with Term B3</td>
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Issues Identified and Consensus Process

Presenter: Dr. Krista Lanctôt
Senior Scientist
Sunnybrook Research Institute
Toronto, ON
Timeline – Developing revised apathy criteria

- Literature Review (Past definitions/criteria): COMPLETED
- Preliminary Survey Development, Circulation, Analysis: COMPLETED
- Feedback from ISCTM, FDA and EPA workshops used to develop final survey
- Survey 1 – Draft Criteria Development, Circulation, Analysis:
  - Target Date: April – June 2018
- AAIC July 2018 – Final Criteria International Consensus Meeting
Key questions from survey

• Should the terminology of ‘apathy’ be changed?
• Should the terminology of ‘emotion’ (criterion B3) be changed?
• What, if anything, distinguishes apathy from depression and anhedonia?
• Are there additional considerations to have apathy as an indication for treatment?
• Assessment of apathy: caregiver, patient and/or clinician?
Should the terminology of ‘apathy’ be changed?

• The philosophical meaning of apathy is “lack of passion”, the latter being an extreme form of emotion

• The contemporary psychiatric meaning of apathy is “loss, lack or impairment of the power to will or execute what is in mind”
Marin (1990, 1991a, 1991b)

- First to recognize clinical utility of identifying different states of apathetic presentation in disorders like dementia, delirium, depression and akinesia (1990).

- Differentiated between apathy as a syndrome vs. symptom (1991a).
  - Syndrome = a primary absence of motivation, or lack of motivation not attributable to disturbance of intellect, emotion, or level of consciousness. Characterized by reduction in the following:
    - Goal-directed overt behaviour (productivity, effort, socialization)
    - Goal-directed cognition (interests, concern)
    - Accompanying emotions (flat affect, responsivity)
  - Symptom = Loss of motivation due to disturbance of intellect, emotion, or level of consciousness.

- Apathy Evaluation Scale (AES) first tool tailored to measure apathy as a neuropsychiatric symptom. Distinguish apathetic patients from normal controls, depressed individuals and other groups (1991b).

- AES-C 0.94 interrater reliability, and both self- and clinician- administered AES distinguished between apathy and depression
Should the terminology of ‘emotion’ (criterion B3) be changed?

Domain B3: Loss of, or diminished, emotion as evidenced by at least one of the following:

- Loss of spontaneous emotion, observed or self reported
- Loss of emotional responsiveness to positive or negative stimuli or events
Overlap between apathy and depression

• apathy and depression both share predicate of “reduced volition” (in the etymological sense of “acting an intention”), which automatically implies a phenomenological overlap
• Depression occurs in the absence of apathy, provided depressed individuals show mood-congruent emotional changes
• Apathy occurs in the absence of depression provided the changes in volition do not co-occur with the emotional changes of depression

Starkstein et al JNNP 2004
Anhedonia and apathy

- Anhedonia—inability to experience pleasure from activities usually found enjoyable
- Apathy is primarily loss of motivation, loss of interest in the environment, and affective dullness.
- Anhedonia is the state in which one cannot derive essential pleasures from behaviors and activities that were joyfully performed in the past i.e., a state where sensitivity to pleasure has decreased
- Anhedonia is the state in which only “loss of pleasure” is manifest, but not “loss of interest”

Kaji and Hirata 2011
Key questions from survey

• Should the terminology of ‘apathy’ be changed?
• Should the terminology of ‘emotion’ (criterion B3) be changed?
• What, if anything, distinguishes apathy from depression and anhedonia?
• Are there additional considerations to have apathy as an indication for treatment?
• Assessment of apathy: caregiver, patient and/or clinician?
Summary – Part 1 (Questions 1&2)

• **Question 1 – keeping the term ‘apathy’:**
  • Most agree to continue labelling as ‘apathy’, and to revise definition, and ensure that we all agree on the operationalization of this term.

• **Question 2 – keeping the term ‘emotion’:**
  • Similarly to the survey, there is some mixed responses here, but overall most agree to change as this term may be too heterogeneous, and may include mood symptoms

• **Suggestions:**
  • Loss of emotional responsiveness
  • Loss of emotional expressiveness
  • Emotional blunting
  • Affect (this was brought up by Group 6, as they felt ‘affect’ was more of an external symptom, and ‘emotion’ was more internal. But they did say that it needs to be determined whether these symptoms are congruent or not)
Summary – Part 2

• **Question 3 – apathy vs. depression vs. anhedonia**
  - All agree that apathy and depression are different and distinct from one another
  - Some differences with apathy vs. anhedonia. Some groups feel that anhedonia should not even be discussed as this is distinct from apathy. However, others feel that anhedonia may be a subcomponent of apathy.

• **Question 4 – apathy as an indication for a tx**
  - Need a clearer idea of the neural circuity/neurobiology of apathy in dementia, and if there are any differences from other population groups (ie: schizophrenia)
  - Group 6 had some suggestions that can be implemented in clinical trials. But overall, they feel that indication may be largely dependent on the ‘context of use’ (ie: treating apathy earlier in disease course, rather than in later stages)

• **Question 5 – assessment of apathy**
  - Most agree that patient, caregiver and clinician reports are important, but caregiver and clinician reports are the most important
  - When choosing a caregiver, need to ensure if this is a ‘good’ caregiver (ie: spends adequate time with the patient, objective)