Making Sense of the Matrix:
A Qualitative Assessment and Commentary on Connecting Psychiatric Symptom Scale Items to the Research Domain Criteria (RDoC)

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ABSTRACT

The Research Domain Criteria (RDoC) initiative aims to organize research according to domains of brain function. Dysfunction within these domains leads to psychopathology that is classically measured with rating scales. Examining the correspondence between the specific measures assessed within rating scales and RDoC domains is necessary to assess the needs for new RDoC-focused scales. Such RDoC-focused scales have the potential of allowing translation of this work into the clinical domain of measuring psychopathology and designing treatment. Here, we describe an initial qualitative assessment by a group of 10 clinician-scientists of the alignment between RDoC domains and the items within five commonly used rating scales. In this commentary, we report limited correspondence and make recommendations for future work needed to address these limitations.

KEYWORDS: Research domain criteria, mental disorder, depression, anxiety, psychosis, rating scales

In 2009 the United States (US) National Institute of Mental Health (NIMH) launched the Research Domain Criteria (RDoC) initiative to provide a new and transformative framework for orienting research on mental disorders.[1] Unlike most conventional nosological systems that focus on syndromal classification based on symptoms, such as the Diagnostic and Statistical Manual (DSM) or International Classification of Diseases (ICD), the RDoC prioritizes basic dimensions of functioning that span the full range of human behavior, from normal to abnormal, and proposes that these dimensions be probed across units of analyses (e.g., molecules, cells, circuits, physiology, observable behavior, and self-reported experiences). The RDoC strategy includes molecular, cellular, circuit, and behavioral functions and identifies precise probes associated with abnormal behavior, promising to lead to a better understanding of the biological processes that underlie mental illnesses and provide the basis for more targeted treatments. The conventional diagnostic systems (DSM, ICD)

have improved reliability of diagnoses, but their major limitations persist, including significant overlap of syndromes that creates apparent "comorbidity," substantial heterogeneity, and lack of validity with respect to biological correlates, pathophysiology, or direction for novel treatment development. Despite these limitations, the conventional diagnoses continue to guide treatment recommendations and form the basis of decision-making and trial designs underlying approval of new treatments by medical regulatory agencies, though there is an increasing openness to considering RDoC-related symptom constructs in labeling.[2]

While RDoC's immediate goals are to deepen the understanding of neurobiological underpinnings of psychiatric disorders, the ultimate goal is to inform and transform therapeutic developments for mental disorders.[3] The ideal outcome to emerge from this initiative would be to have measurable, precise alterations across an RDoC domain or subdomain that can be specifically addressed with targeted interventions. These interventions would likely differ across individuals who currently share the same diagnostic category per DSM. Thus, fundamentally, the progress envisioned by RDoC is closely related to the vision for precision medicine promoted by the US National Institutes of Health (NIH).[4]

An interesting feature of RDoC is that among its units of analysis, the symptoms most critical to conventional diagnosis are not explicitly included. Self-reports might include symptom rating scales, but in general, this unit of analysis so far has not included the criterion symptoms in the DSM nor the instruments that are used to assess these symptoms in mental health research. While progress is being made for evaluating the components of the matrix of RDoC in other units of analysis, one area that merits attention is the level of correspondence between the diagnosis-focused clinical scales used to measure therapeutic benefit and the

domains of function studied under RDoC. Decades of DSM-based research using well-established symptom scales has produced large clinical datasets, with associated biological data that could be mined to yield new insights if the rating scales can be aligned with RDoC constructs. How well do the most commonly used rating scales, for which comparative changes lead to the approval of new therapies, serve the purpose of measuring RDoC constructs and response to interventions based on the RDoC framework? The six functional domains, as currently defined by RDoC, are Negative Valence Systems (NVS), Positive Valence Systems (PVS), Cognitive Systems (CS), Social Processes (SP), Arousal and Regulatory Systems (ARS), and Sensorimotor Systems (SS),[5] are agnostic to DSM diagnosis and not targeted at symptoms; thus, it is possible that current rating scales will not be useful for assessing behavior and symptoms within the RDoC domains most relevant to specific diseases. In this regard, it is possible that they would require reconfiguration and reorganization according to RDoC domains (for an initial example, see Khazanov et al[6]). Understanding this correspondence, or lack thereof, is critical for moving forward and, eventually, best applying the benefits of the RDoC initiative to inform the design of clinical trials and ultimately impact on clinical care. At that point in time, a new characterization of therapeutic response, with new rating scales rooted in RDoC domains or subdomains, and new FDA guidance will be needed. In the meantime, however, information providing an initial proof of concept might be obtained from exploratory re-analyses of currently available clinical trials data considering domain specific subsets of rating scales.

In pursuit of this goal, this commentary describes the process and outcomes of an effort to examine the correspondence between RDoC domains and elements of commonly used clinical rating scales by a group of 10

experts with clinical and research expertise across different disease areas and experimental methodologies. These experts come from varying academic and research backgrounds and have a range of preclinical and clinical experience, including psychopathology, pharmacology, clinical trials, imaging, neuropsychological and biomarker evaluation, psychosocial and workplace functioning, and social cognition. All have a demonstrated interest in the utilization of the theoretical framework examining domains of behavior within their areas of research, as evidenced by their ongoing studies and their prior publications, such as examining predictors for response to antidepressant medication.[7,8]

METHODS

A group of 10 researchers (LC, AAD, RMB, BWD, PDH, DAP, CAT, RSM, JMK and Madhukar Trivedi) were tasked with assigning over 100 line-items taken from a set of seven rating scales frequently used in clinical trials for depression and psychosis to one of the six RDoC domains. The following rating scales were selected: Montgomery-Asberg Depression Rating Scale (MADRS);[9] 17-item Hamilton Depression Rating Scale (HAM-D17);[10] Inventory of Depressive Symptomatology, Self-Report (IDS-SR);[11] Hamilton Anxiety Rating Scale (HAM-A);[12] Sheehan Disability Scale (SDS);[13] Positive and Negative Syndrome Scale (PANSS);[14,15] and the Personal and Social Performance (PSP) Scale.[16] The group completed their assignment through a two-stage process in which they first assigned, via a digital platform (Radius Direct), each item of these rating scales to a specific RDoC domain. The instructions were to attempt to assign a single domain or subdomain to each item in the scales, although the online platform allowed participants to assign an item to more than one domain. Initial consensus was calculated based on the online feedback. As participants

TABLE 1. Initial consensus after online voting: consensus achieved for 42 items

RDoC	MADRS	HAM-D17	IDS-SR	HAM-A	PANSS
Negative valence systems	10. Suicidal thoughts	1. Depressed mood 10. Anxiety (psychic) 11. Anxiety (somatic)	5. Feeling sad 18. Thoughts of death or suicide	1. Anxious mood 3. Fears 6. Depressed mood	G2. Anxiety
Positive valence systems	8. Inability to feel	N/A	8. Response of your mood to good or desired events 21. Capacity for pleasure or enjoyment (excluding sex) 22. Interest in sex (interest, not activity)	N/A	N/A
Cognitive systems	6. Concentration difficulties	N/A	15. Concentration/decision making	5. Intellectual	P2. Conceptual disorganization P3. Hallucinatory behavior N5. Difficulty in abstract thinking N6. Lack of spontaneity and flow of conversation N7. Stereotyped thinking G9. Unusual thought content G10. Disoreintation G11. Poor attention
Social processes	N/A	N/A	N/A	N/A	N3. Poor rapport
Arousal/ regulatory systems	4. Reduced sleep	4. Insomnia (early in the night) 5. Insomnia (middle of the night) 6. Insomnia (early hours of the morning)	1. Falling asleep 2. Sleep during the night 3. Waking up too early 4. Sleeping too much 9. Mood in relation to time of day 20. Energy level	4. Insomnia 9. Cardiovascular symptoms 13. Autonomic symptoms	N/A
Sensorimotor systems	N/A	N/A	23. Feeling slowed down	N/A	G5. Mannerisms and posturing G7. Motor retardation

HAM-A: Hamilton Anxiety Rating Scale; HAM-D17: 17-item Hamilton Depression Rating Scale; IDS-SR: Inventory of Depressive Symptomatology, Self-Report; MADRS: Montgomery-Asberg Depression Rating Scale; PANSS: Positive and Negative Syndrome Scale; RDoC: Research Domain Criteria; N/A: not applicable

placed some items in more than one domain, consensus could not be defined only by the greatest percentage of votes out of 10 participants. Therefore, the initial definition of consensus was operationalized as all of the following: a selection made by at least five of the 10 participants, a selection that received 40 percent or more of the total votes, and a selection had to be separated from the next most frequent domain selection by more than 10 percent of the votes and had to have fewer than five votes for that next most frequent domain selection.

This process was then followed by a live meeting to reach consensus on assigning all items. As part of that discussion, it was agreed that two of the scales, the SDS and the PSP, should be removed from consideration because they evaluate functional performance, rather than psychopathology, and have limited validity and utility, particularly when measured over short time periods.[17] In addition, the group felt individual items of the SDS could be allocated across multiple RDoC

domains, thus lacking specificity. Moreover, self-reports of everyday functioning across samples of participants meeting criteria for different DSM diagnoses have been shown to have limited correlation with objective reports or performance-based assessments of functionality and to be influenced by current mood states.[18–22] Finally, the PSP does not provide clear guidance on how information should be obtained for ratings, thus leading to a situation where similar scores on the PSP could originate from completely different information sources.[23]

RESULTS

When the initial online results were tabulated using the consensus definition and following the removal of the SDS and PSP from the task (7 items), the group was able to reach initial consensus through the online survey for 42 of the remaining 101 items (Table 1) that spanned across the five remaining scales (MADRS, HAM-D17, IDS-SR, HAM-A, and PANSS).

The best example of consensus was reached for the RDoC domain of NVS, where the group was able to place select items from the five scales related to depressed or sad mood and anxiety. For CS, the group reached the consensus definition for items from the five scales, with the predominant items being from the PANSS across the positive, negative, and general psychopathology subscales related to judgement, conceptual organization, and abstract thinking. Both the ARS and SS domains were assigned items from the five scales mostly related to the sleep/wake cycle and general arousal. However, for both PVS and SS there was more variability in the initial online voting, leading to discussions during the consensus meeting. At that meeting, the group reached consensus on the primary RDoC domain for 50 additional scale items, for a total of 92 items from the five remaining scales (Table 2). The cognition and arousal RDoC domains had the greatest number of scale items reaching consensus, and each accounted for over 20 percent of the total items, with less than 10

TABLE 2. Final consensus: consensus achieved for 92 items[a]

RDoC	MADRS	HAM-D17	IDS-SR	HAM-A	PANSS
Negative valence systems	1. Apparent sadness 2. Reported sadness 3. Inner tension 10. Suicidal thoughts	1. Depressed mood 10. Anxiety (psychic) 11. Anxiety (somatic)[b] 15. Hypochondriasis	5. Feeling sad 6. Feeling irriatable 7. Feeling anxious or tense 18. Thoughts of death or suicide	1. Anxious mood 3. Fears 6. Depressed mood	G2. Anxiety G6. Depression
Positive valence systems	8. Inability to feel	7. Work and activities 14. Genital symptoms	8. Response of your mood to good or desired events 21. Capacity for pleasure or enjoyment (excluding sex)	17. View of my future 19. General interest 22. Interest in sex (interest, not activity)	N/A
Cognitive systems	6. Concentration difficulties	2. Feelings of guilt 16. Insight	15. Concentration/decision making	5. Intellectual	P1. Delusions P2. Conceptual disorganization P3. Hallucinatory behavior P5. Grandiosity P6. Suspiciousness/persecution N5. Difficulty in abstract thinking N6. Lack of spontaneity and flow of conversation N7. Stereotyped thinking
Social processes	N/A	N/A	16. View of myself 29. Interpersonal sensitivity	N/A	P7. Hostility N1. Blunted affect[b] N3. Poor rapport N4. Passive/apathetic social withdraw
Arousal/regulatory systems	4. Reduced sleep 5. Reduced appetite	4. Insomnia (early in the night) 5. Insomnia (middle of the night) 6. Insomnia (early hours of the morning) 9. Agitation 15. Hypochondriasis[b] 16. Loss of weight	1. Falling asleep 2. Sleep during the night 3. Waking up too early 4. Sleeping too much 9. Mood in relation to time of day	11. Decreased appetite 12. Increased appetite 13. Decreased weight 14. Increased weight 20. Energy level 24. Feeling restless	2. Tension 4. Insomnia 9. Cardiovascular symptoms 13. Autonomic symptoms 14. Behavior at interview[b]
Sensorimotor systems	7. Lassitude	8. Retardation 15. Hypochondriasis[b]	23. Feeling slowed down 30. Leaden paralysis/physical energy	14. Behavior at interview[b]	G5. Mannerisms and posturing

[a]Items featured in this table consist of all line items for which consensus was reached from 5 out of 7 clinical scales assessed during the live advisory board (line items are organized by the primary domain to which they have been allocated).
[b]Line item corresponding to two co-primary domains due to equal votes during the individual ranking segment of the live advisory board meeting
HAM-A: Hamilton Anxiety Rating Scale; HAM-D17: 17-item Hamilton Depression Rating Scale; IDS-SR: Inventory of Depressive Symptomatology, Self-Report; MADRS: Montgomery-Asberg Depression Rating Scale; PANSS: Positive and Negative Syndrome Scale; RDoC: Research Domain Criteria; N/A: not applicable

percent of the items placed in each of the sensorimotor and social domains.

During the live discussion, the group identified three types of challenges that arose in matching scale items to RDoC domains, categorized into three sections: 1) Items that fit into multiple domains; 2) Items that could not be assigned to any domain (general somatic symptoms); and 3) "Difficult to classify" items.

Items that fit into multiple domains.
Most items could not be assigned to a single domain, as they informed multiple domains. While the consensus definition was reached in the online voting for 41.6 percent of the items, upon meeting live, the group felt there was justification for more than one RDoC domain

for many of the items because of the breadth of their definition. For this reason, the group decided most items should be assigned to both a primary and a secondary domain. For example, MADRS Item 2, reported sadness, contains elements of both NVS and PVS domains in its description. The description states, "representing reports of depressed mood, regardless of whether it is reflected in appearance or not." It includes low spirits, despondency, or the feeling of being beyond help without hope, which justifies classification within the NVS, consisting of loss, sustained threat, and frustrative nonreward. The description also recommends rating the item according to intensity, duration, and the extent

to which the mood is reportedly influenced by events, which fits the description of PVS, including reward responsiveness and reward valuation.[24]

RDoC domains and line items were evaluated as written; thus, an additional challenge in parsing out the items was the interpretation of an item's description. The group agreed to interpret the intent of each line item based on its description as written to avoid assumptions regarding the etiologies, biological or psychological, of the symptom. Assignment of the items could be influenced by how the measurement is made, whether by subjective report or objective assessment. For example, the NVS domain appears to be predominantly

involved when the scale requires an individual to give a subjective report regarding their mental experience. In contrast, an objective assessment by a rater or clinician might not categorize those symptoms as part of the NVS domain and, as noted in the example above, the objective rater assessment would yield a different result.

Moreover, similar line items from separate scales were assigned to different domains, as their specific descriptions differed. Because the group interpreted the item descriptions as written, many items that superficially appeared similar across scales were assigned to different RDoC domains, suggesting variability in the detailed descriptions of a specific symptom across scales. Some examples of similar-appearing items leading to diverging RDoC domain assignments were tension, sadness, psychomotor retardation, activity, guilt, insight, self-perception, social withdrawal, and thought disorder. Table 3 outlines the details regarding these items. These examples, and the others described earlier, illustrate the challenges in assigning rating scale items to single RDoC domains and subdomains. Development of new scales that align more closely with RDoC domains might be necessary in the future to apply the concepts from RDoC into clinical applications.

Items that could not be assigned to any domain (general somatic symptoms). General somatic symptoms need to be integrated into the RDoC matrix; however, the framework needs to be further developed to incorporate these items. Upon discussion, the group agreed that items in the HAM-D17, IDS-SR, and HAM-A describing general somatic symptoms did not fit into the current RDoC framework. The inability to make RDoC classifications of these symptoms commonly experienced across DSM disorders led the group to consider the value of adding an interoception domain to the RDoC matrix. This new domain would encompass self-monitoring and self-perception of somatic sensations, such as pain and other symptoms. Substantial research supports the neurobiology of interoceptive processing, disruptions of which might be relevant across psychiatric illnesses and treatments.[24,25]

Additional components that were suggested for this domain included self-assessment of the quality of actions and decisions, social

cognitive understanding of scenarios, and the ability to learn and perform skilled acts, a critical deficit in many severe mental illnesses.

"Difficult to classify" items. Many items were challenging to classify into RDoC categories. These items remain highly clinically relevant. For example, items related to suicide, such as the HAM-D Item 3, suicide, include a wide span of symptoms, from anticipatory affect, cognitive ideation to impulsivity and actual suicide attempts, which involve taking an action. NVS, CS, and PVS were all considered by the group without reaching an agreement. Similar difficulty was encountered for the MADRS pessimistic thoughts item. Experts thought it could be allocated to NVS, PVS, CS, and SP if extreme dysfunctions occur within any of these domains. Additional items for which consensus could not be reached included the IDS-SR items feeling irritable, quality of your mood, view of my future, and general interest.

Several PANSS items also yielded difficulties in classification. For the PANSS Item P1, delusions, CS was selected as the primary domain because of the item's description of cognitive distortions. SP was selected as the secondary domain because the item description evaluated the effect of delusions on social interactions and behavior. For the PANSS Item G8, uncooperativeness, advisors selected SP as the primary domain but could not agree on a secondary domain because the description was too broad. For the PANSS Item G14, poor impulse control, CS and SS were selected as co-primary domains because the line item's description contains mention of cognitive control, executive motor planning, and motor inhibition of volitional activity. ARS was selected as the secondary domain because the description contains elements of the hair-trigger response. The PANSS Item P7, hostility, was assigned to SP as primary domain because the description contains elements of social communication. Advisors agreed that the basis for rating was observed behavior as opposed to patient perception of their behavior. Additional potential domains for this item included NVS, PVS, and CS. Item N2, emotional withdrawal, was assigned to PVS as the primary domain because the item's description contained elements of anhedonia. SP was selected as the secondary domain.

DISCUSSION

To the best of our knowledge, this is the first attempt at linking RDoC to commonly used clinical rating scales. Here, we performed a qualitative review of the items from five widely used clinical scales to examine how well they correspond to RDoC domains. We showed that rating scales have limitations in their applicability to RDoC domains. This is not surprising, considering that, fundamentally, the RDoC is agnostic to the phenomenologically based DSM definitions of mental disorders and the similarly anchored clinical rating scales currently in use.

We noted that some rating scale items fit into multiple domains. It is possible that the same behavioral manifestation can relate to multiple domains due to an actual overlap in brain mechanisms, leading to similar behavioral expression reflected in one item. For example, there is significant overlap between CS and SS regarding cognitive control, executive motor planning, and motor inhibition. Another potential explanation is a deficiency in the description of the items themselves, rendering them imprecise or ambiguous; revision of the item descriptors and/or basis for ratings could, however, negatively alter the scale's psychometric properties.

Another observation is that some items of high clinical importance, such as suicide, did not fit into any RDoC domain. Similarly, self-destructive behavior, impulsivity, and risk taking were difficult to classify. These are important dimensions of behavior that should be captured within the RDoC matrix if it is to become a tool to guide clinical evaluation. This raises the question of whether additional RDoC constructs should be developed to obtain information on clinical aspects that are presently not represented. A similar consideration applies to somatic symptoms and interoception.

As noted above, RDoC does not capture self-perception and response biases, which could be linked to a variety of functional outcomes and might also be implicated in suicidal ideation and behavior.

A question that arises from this exercise is whether further development of the RDoC framework would benefit from the creation of new rating scales that are specific to discrete domains, avoiding overlap between domains. This could start by regrouping items from

TABLE 3. Similar-appearing items leading to diverging RDoC domain assignments

ITEM	COMMENTARY
Tension	The symptom of tension, IDS-SR Item 7, feeling anxious/tense, and PANSS Item G4, tension, appear similar. Yet, the IDS-SR Item 7, feeling anxious/tense, was assigned to NVS as primary and ARS as secondary domain. In contrast, PANSS Item G4, tension, was assigned to ARS as primary and NVS as secondary domain. This difference in assignment was due to the presence of "physical manifestations of fear, anxiety, and agitation, such as stiffness, tremor, profuse sweating, and restlessness" in the line item's description of PANSS Item G4, tension, which was not present in the IDS-SR Item 7. Similar discrepancies in descriptions resulted in the MADRS Item 3, inner tension, being assigned to NVS/ARS (along with IDS-SR Item 7), whereas the HAM-A Item 2, tension, mapped onto ARS/NVS (along with PANSS Item G4) because their descriptions emphasized trembling and restlessness.
Sadness	The apparent sadness and reported sadness items in the MADRS and the depression item in the PANSS were also placed into different RDoC domains. While these would appear to be similar at face value, and the group placed these all primarily in the NVS domain, apparent sadness was placed secondarily in SP and the other items in PVS. Apparent sadness emphasized elements of the communicative aspect of sad affect, suggesting social processes were a component of the assessment for this item, compared to the other two items. For the PANSS item depression, the basis for rating is explicitly given as "verbal report of depressed mood during the interview and its observed influence on the patient's attitude and behavior as reported from primary care workers or family."
Psychomotor retardation	The HAM-D17 item retardation was allocated to the SS domain as primary due to its emphasis on motor speed and the CS domain as secondary due to its description of slowness of thought and speech and inability to concentrate. In addition, the description mentions stupor, which could potentially justify placing it into the ARS domain, as it is congruent with the element of coma, a low arousal state, though this level of retardation is rarely encountered. This observation demonstrates the challenge for some rating scale items for which extreme severity can result in changes in the apparent best matching RDoC domain.
Activity	The MADRS item lassitude and IDS-SR item leaden paralysis/physical energy both fit best with SS followed by ARS. Strong consistency was observed for the IDS-SR item feeling restless, the HAM-D17 item agitation, and the PANSS Item P4, excitement, all placed in ARS as for primary and SS domain secondarily. ARS was justified by the line items' descriptions of locomotor activity. SS was not selected as primary because the descriptions do not contain elements of the motor action construct, such as action planning, sensorimotor dynamics, initiation, and execution.
Guilt	The HAM-D17 item feelings of guilt and the PANSS Item G3, guilt feelings, were placed in CS and SP. CS was selected as the primary domain because the items' descriptions for the higher levels of severity contain elements of delusions, a form of cognitive distortion. SP was selected as the secondary domain because the item's description contains elements of the perception and understanding of self construct. For PANSS Item G3, guilt feelings, SP was selected as the secondary domain because the item includes elements of communication, such as verbal report of guilt feelings and the influence of thoughts and attitudes on those feelings. Experts agreed that cognitive distortions would fall into the language construct of the CS domain, as it encompasses a system of shared symbolic representations of the world, the self, and abstract concepts that support thought and communication.
Insight	The HAM-D17 Item 17, insight, and the PANSS Item G12, lack of judgment and insight, were assigned to CS as primary and SP as secondary domain because the items' descriptions contain elements from the perception and understanding of self construct within the SP domain.
Self-perception	The IDS-SR Item 16, view of myself, and Item 29, interpersonal sensitivity, were assigned to SP and NVS. SP was selected as the primary domain because the items' descriptions contain elements from the perception and understanding of self construct, including judgments of self, such as self-awareness, self-monitoring, and self-knowledge. NVS was selected as the secondary domain because the item's description contains elements of negative view of self and presence of self-blame, or the acute threat (fear) construct, including perceived threat, respectively.
Social withdrawal	The PANSS Item N4, passive/apathetic social withdrawal, and Item G16, active social avoidance, were assigned to SP as the primary domain because the items' descriptions contain elements of diminished social interest and initiative and the effect that this has on interpersonal interactions. A second domain for this item was not selected because advisors agreed that it would vary depending on the observer (N4) or mechanisms associated with the underlying causes of the symptoms (G16). The basis for rating for PANSS Item N4 or Item G16 is explicitly given as "social behavior reports from primary care workers or family" only, thus not directly from the patient nor behaviors directly observed during the interview.
Thought disorder	PANSS Item G15, preoccupation, and PANSS Item P6, suspiciousness/persecution, were assigned to CS and SP. CS was selected as the primary domain because the items' descriptions include elements of cognitive distortions. SP was selected as the secondary domain because the basis for rating the items is interpersonal behavior observed during the interview. Experts discussed the addition of NVS for PANSS Item P6, as an additional secondary domain because the item's description contains mention of distrustful attitude, suspicious hypervigilance, and guardedness as outcomes of fear and sustained threat.

ARS: Arousal/regulatory systems; CS: Cognitive systems; HAM-A: Hamilton Anxiety Rating Scale; HAM-D17: 17-item Hamilton Depression Rating Scale; IDS-SR: Inventory of Depressive Symptomatology, Self-Report; MADRS: Montgomery-Asberg Depression Rating Scale; NVS: negative valence systems; PANSS: Positive and Negative Syndrome Scale; PVS: positive valence systems; RDoC: Research Domain Criteria; SP: social processes; SS: sensorimotor systems

existing scales based on a statistical assessment of which items relate best to which domain. Some work is already underway. A group of researchers developed a PVS scale of 21 items measuring responses to a wide range of rewards, including food, physical touch, being outdoors, positive feedback, social interactions, hobbies, and goals.[6] This scale showed good validity, factorial reliability, and internal consistency and was better related to reward than negative valence, depression, or anxiety. This type of work should extend to other domains and subdomains. Applying natural language processing to questionnaire data using word embeddings is another approach that might enable use of existing questionnaire datasets to address RDoC approaches to mental illness.[26]

Limitations. A limitation of this exercise was that scale items were linked only to the level of RDoC domain, even though each domain subsumes several constructs. For example, NVS includes anxiety, fear, and loss, each of which has been linked to separate biological features, though our classifications of the scale items linked only to the domain level. A further limitation of the scales, which is tacit

to the limitations of RDoC, is that the scales do not have the ability to consider potential changes in phenomenology across the illness trajectory.[27,28]

CONCLUSION

The RDoC is a novel approach to understanding brain function and dysfunction that leads to abnormal symptoms and behavior. Our main recommendations include quantitative testing of the correspondence between rating scale items and RDoC subdomains using statistical methods, followed by development of more specific rating scales to capture RDoC subdomains and examination of therapeutic efficacy of agents available and in development with these new scales by using large data sets derived from clinical trials. Better alignment of the transformative RDoC initiative with contemporary clinical trial methodology will benefit both fields and ultimately translate into a larger impact on optimizing health for our most vulnerable patients.

REFERENCES

1. 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(7):748–751.
2. Sanislow CA, Ferrante M, Pacheco J, et al. Advancing translational research using NIMH research domain criteria and computational methods. *Neuron*. 2019;101(5):779–782.
3. Sanislow CA. RDoC at 10: changing the discourse for psychopathology. *World Psychiatry*. 2020;19(3):311–312.
4. Collins FS, Varmus H. A new initiative on precision medicine. *N Engl J Med*. 2015;372(9):793–795.
5. National Institute of Mental Health. RDoC matrix. https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/constructs/rdoc-matrix. Accessed 19 Jan 2022.
6. Khazanov GK, Ruscio AM, Forbes CN. The positive valence systems scale: development and validation. *Assessment*. 2020;27(5):1045–1069.
7. Ang YS, Kaiser R, Deckersbach T, et al. Pretreatment reward sensitivity and frontostriatal resting-state functional connectivity are associated with response to bupropion after sertraline nonresponse. *Biol Psychiatry*. 2020;88(8):657–667.
8. Ahmed AT, Frye MA, Rush AJ, et al. Mapping depression rating scale phenotypes onto research domain criteria (RDoC) to inform biological research in mood disorders. *J Affect Disord*. 2018;238:1–7.
9. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134:382–389.
10. Khan A, Khan SR, Shankles EB, Polissar NL. Relative sensitivity of the Montgomery-Asberg Depression Rating Scale, the Hamilton Depression rating scale and the Clinical Global Impressions rating scale in antidepressant clinical trials. *Int Clin Psychopharmacol*. 2002;17(6):281–285.
11. Rush AJ, Giles DE, Schlesser MA, et al. The Inventory for Depressive Symptomatology (IDS): preliminary findings. *Psychiatry Res*. 1986;18(1):65–87.
12. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol*. 1959;32(1):50–55.
13. Leon AC, Olfson M, Portera L, Farber L, Sheehan DV. Assessing psychiatric impairment in primary care with the Sheehan Disability Scale. *Int J Psychiatry Med*. 1997;27(2):93–105.
14. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bull*. 1987;13:261–276.
15. Kay SR, Opler LA, Fiszbein A. *Positive and Negative Syndrome Scale (PANSS) Technical Manual*. MultiHealth Systems, Inc.: Toronto, Ontario; 2006.
16. Morosini PL, Magliano L, Brambilla L, et al. Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. *Acta Psychiatr Scand*. 2000;101(4):323–329.
17. Weiller E, Weiss C, Watling CP, et al. Functioning outcomes with adjunctive treatments for major depressive disorder: a systematic review of randomized placebo-controlled studies. *Neuropsychiatr Dis Treat*. 2018;14:103–115.
18. Kaye JL, Dunlop BW, Iosifescu DV, et al. Cognition, functional capacity, and self-reported disability in women with posttraumatic stress disorder: examining the convergence of performance-based measures and self-reports. *J Psychiatr Res*. 2014;57:51–57.
19. Strassnig M, Kotov R, Fochtmann L, et al. Associations of independent living and labor force participation with impairment indicators in schizophrenia and bipolar disorder at 20-year follow-up. *Schizophr Res*. 2018;197:150–155.
20. Yoo-Jeong M, Anderson A, Rahman AF, et al. Associations of mood on objective and subjective cognitive complaints in persons living with HIV/AIDS. *J HIV AIDS*. 2018;4(1): 10.16966/2380-5536.146.
21. Strober LB, Binder A, Nikelshpur OM, et al. The perceived deficits questionnaire: perception, deficit, or distress? *Int J MS Care*. 2016;18(4):183–190.
22. Sumiyoshi T, Watanabe K, Noto S, et al. Relationship of cognitive impairment with depressive symptoms and psychosocial function in patients with major depressive disorder: cross-sectional analysis of baseline data from PERFORM-J. *J Affect Disord*. 2019;258:172–178.
23. Schaub D, Brune M, Bierhoff HW, Juckel G. Comparison of self- and clinician's ratings of personal and social performance in patients with schizophrenia: the role of insight. *Psychopathology*. 2012;45(2):109–116.
24. Khalsa SS, Adolphs R, Cameron OG, et al. Interoception and mental health: a roadmap. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2018;3(6):501–513.
25. Khoury NM, Lutz J, Schuman-Olivier Z. Interoception in psychiatric disorders: a review of randomized, controlled trials with interoception-based interventions. *Harv Rev Psychiatry*. 2018;26(5):250–263.
26. Sonabend WA, Pellegrini AM, Chan S, et al. Integrating questionnaire measures for transdiagnostic psychiatric phenotyping using word2vec. *PLoS One*. 2020;15(4):e0230663.
27. McIntyre RS. In vivo phenotyping, mechanism-informed treatments, domain-based psychopathology and nomological networks: a strategy for treatment discovery and development in bipolar depression. *Bipolar Disord*. 2020;22(7):657–659.
28. Tai AMY, Albuquerque A, Carmona NE, et al. Machine learning and big data: implications for disease modeling and therapeutic discovery in psychiatry. *Artif Intell Med*. 2019;99:101704. **ICNS**