Integrating an ontology for RDOC with existing biomedical ontologies

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ABSTRACT
The Research Domain Criteria (RDoC) is an initiative developed by the National Institute of Mental Health (NIMH) to guide research and facilitate better communication about mental disorders, and psychopathology in general. Recent advances in neuroscience have not offered significant improvement in treatment modalities and patient care for people afflicted with mental health problems. The RDoC project is an attempt to address the heterogeneity of diagnostic categorizations and the lack of progress in research into the neurobiological foundations of mental disorders. The core of RDoC is based on a Matrix in which functional aspects of behavior, named Constructs, are related to genetic, neurological, and phenotypic research findings, along with the various assays, self-reports and paradigms that generate the data used to make such findings. The RDoC Matrix suffers from several problems, which need to addressed before it can deliver on the NIMH's long-term goals of fostering translational research via the broad sharing of data relevant to psychopathology. One of the most difficult challenges for RDoC is in providing researchers and users of the Matrix a formalized unambiguous way of linking findings in genetics, molecular biology, and neuroscience to the constructs for which they are thought to be associated. The purpose of this paper is to discuss those challenges. We expand our previous analysis of the RDoC matrix and introduce an ontological representation of the Constructs, the RDoC Ontology (RDoCOn), that provides a method for incorporating the RDoC framework with current biomedical ontologies. We demonstrate a way in which particular Elements in the Matrix can be usefully linked to Constructs.

1 INTRODUCTION

The Research Domain Criteria (RDoC) is an initiative developed by the National Institute of Mental Health (NIMH) to guide research and facilitate better communication about mental disorders, and psychopathology in general. The NIMH offers RDoC as a framework for conducting research, one that is based on dimensions of observable behaviors and neurobiological measures (NIMH, 2017a). RDoC has been developed to address the lack of significant progress towards the discovery of the neurobiological foundations of mental disorders, even as the global burden of mental health-related problems is at an all-time high. Conceived as a "new paradigm" for understanding psychopathology, RDoC attempts to solve this on-going problem by reconceiving the methodology researchers use to design and conduct experiments. The RDoC framework is designed to aid in the identification of neurobiological correlates for the clinical categorizations of mental disorders, and ideally enable significant improvements in treatment modalities and patient care (Cuthbert, 2010).

The clinical categorizations of mental disorders as seen in the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Disease (ICD) repeatedly fail to correlate with valid sets of biomarkers that could be useful for diagnosis or treatment (Cooper, 2004). The DSM and ICD approach are fundamentally rooted in a phenomenological "lumping" approach for grouping together types of observable behaviors and psychological constructs into disjunctive criteria used primarily for diagnostic and coding purposes. This syndromic view of mental disorders suffers from problems of over-inclusion, heterogeneity amongst patients with same diagnosis, lack of construct validity, and treatment and prognostic reliability, among others (First & Wakefield, 2010). RDoC aims to avoid these issues by incorporating a dimensional methodology rooted in findings from neuroscience and genetics. The RDoC framework enables researchers to consider the multifaceted phenomena surrounding psychopathology in a way not limited by the assumptions of disorder continuity built into the DSM or ICD.

The core of RDoC is based on a matrix in which functional aspects of behavior, named Constructs, are related to genetic, neurological, and phenotypic research findings, along with various assays, self-reports and paradigms that generate the data used to make such findings. Grounding the Constructs are eight Units of Analysis: Genes, Molecules, Cells, Circuits, Physiology, Behavior, Self-Report, and Paradigms. Particular Elements, such as brain-derived neurotrophic factor (BDNF), Dopamine, Hypothalamus, Fear Potential Startle, or Drifting Double Bandit, populate the cells for each of the 41 Constructs (Table 1). Central to the long-term aims of NIMH's vison for RDoC is to foster translational science and the broad sharing of data relevant to mental disorders. As part of realizing this goal, an RDoC Database (RDoCdb) has been created (NIMH, 2017b). The creators of RDoC hope to generate a set of standardized paradigms for assessing the Constructs (NIMH, 2016). However, this goal does not address a much broader concern of how exactly the findings in RDoC will be mapped to research conducted outside the framework established by the Matrix.

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Domain	Construct	Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-Reports	Paradigms
Negative Valence Systems	Acute Threat ("Fear")	BDNF	Dopamine	Glia	Central Nucleus	Context Startle	Response inhibition	Fear survey schedule	Stranger Tests
	Potential Threat ("Anxiety")	CRF	Cortisol	Pituitary cells	Bed nucleus of stria terminalis	Potentiated startle			Contextual Threat
	Sustained Threat		ACTH	Hippocampal	Hypothalamic nuclei	Dysregulated HPA axis	Avoidance		
	Loss	COMT	Glucocorticoid receptors		Amygdala	neuroimmune	Anhedonia	Change in attributional style	
	Frustrative Non-reward	5-HTTLPR	GABA		Parasympathetic system		Physical and relational aggression	Buss-Durkee and Buss Perry	Social dominance test

Table 1. An illustration of the RDoC Domain "Negative Valance Systems" with its five Constructs and one example of an Element considered relevant to that construct. Note RDoC does not list any potential Elements for some cells.

In health informatics, there is a clear and demonstrable need to provide standardized, extensible and semantically interoperable solutions for the sharing of data and marking-up of information sources to enhance knowledge discovery. It is widely accepted that modern healthcare requires high-quality information, which is readily accessible, easily searchable, reliably encoded, and stored and structured in such a way as to provide the capability to be automatically manipulated and reasoned over (Hammond, 2014). Ontologies have emerged as one part of the health informatics solution, one which provides an essential role in the standardization, formalization, and computability of terminologies and knowledge management systems.

Perhaps the most visible, and arguably most successful, example of the expanding role of ontologies is the use of the Gene Ontology (GO) in describing the associations of gene products (proteins and RNAs) with biological processes, functions, and cellular components (Ashburner, 2000). The GO is one of the over hundred ontologies that part of the Open Biomedical Ontologies (OBO) Foundry. OBO is a consortium of ontology developers and suite of ontologies that are developed according to a set of explicit guiding principles to ensure reuse, consistency and interoperability (Smith, 2007). GO has been used to annotate gene products with GO terms that describe their molecular functions, cellular localization and biological process associations based on data from experiments discussed in over 100,000 journal articles. The GO annotation process relies at its core upon manual curation of the scientific literature by trained scientists who are familiar with the biological domain under study and are able to interpret scientific data presented in individual research papers in order to create GO annotations that associate a gene product with a GO term. Supervised computational methods are then used to propagate GO annotations for gene products in one species to orthologous gene products in related species to infer GO annotations for gene products in species that require different experimental modalities than those available in the first species. Thus, knockout mouse experiments are often used to provide GO annotations for proteins expressed in the nervous system that are difficult to study directly in humans.

The purpose of this paper is to propose how realism-based methods for developing and utilizing ontologies can be used to support and improve RDoC and its methodology, for example in the linking of GO annotations to research which utilizes the RDoC Matrix. We summarize previous work in which we analyzed the Matrix for terminological and ontological principles. We then illustrate how we have redefined the RDoC constructs as bodily systems which bear functions, and discuss existing resources that can be incorporated, along with their limitations, and what will need to be improved.

2 THE MATRIX

The rows in the Matrix consist of Constructs, which are grouped together into five broad Domains that attempt to represent our current understanding about key psychological systems. The RDoC Domains are: *negative valence systems, positive valence systems, cognitive systems, social process systems, and arousal and regulatory systems*. The columns in the Matrix are the Units of Analysis, which are populated by Elements that are thought to be associated with any particular construct. (Table 1).

We discovered a variety of problems with the matrix as it is currently formulated (Ceusters et al., 2017). Foremost is the lack of face value for several Elements that are used to populate the Matrix. Twelve Elements are listed as both Genes and Molecules, for example, BDNF, Dopamine, Norepinephrine, and Acetylcholine are found in both columns of the Matrix. In other cases, terms are used as Elements that clearly do not refer to a gene or molecule, such as 'opioid system' and 'mouse knockout models'. From this it

is clear that the developers of the Matrix did not have in mind any consistent criteria for determining whether an Element should be listed as a 'Gene' versus a 'Molecule'.

From an ontological perspective, we would like to see clear definitions of what a 'Gene' and 'Molecule' is in the RDoC system. We would suggest that the RDoC system refer to genes in the modern genetic sense of a DNA sequence encoding a protein or functional RNA, and refer to encoded proteins or RNAs directly when particular experimental data address the nature of those types of entities directly. This is particularly important when considering spliced forms of proteins or proteins with different types of post-translational modifications. 'Molecule' might best be reserved for non-polypeptide entities, i.e., specific biochemical or small molecules such as dopamine, norepinephrine, and acetylcholine that play roles in the functioning of the nervous system. For all these entities, appropriate terms should be selected from existing OBO Foundry ontologies.

In addition to there being a lack of clarity in how to determine whether particular Elements belong as Genes or Molecules, there similarly exists overlap between Cells and Circuits, Circuits and Physiology, and Behavior and Paradigms. Furthermore, there is the problem of how to distinguish between all of these Units of Analysis and the Constructs themselves. We contend that this is because RDoC Constructs are not defined well enough to unravel this overlap. For example, 'Animacy Perception' is defined as "the ability to appropriately perceive that another entity is an agent', while the term 'ability to appropriately attribute animacy to other agents' is an Element within the Behavior Unit of Analysis. How would this Element be related to the Construct? Via equivalency? It would seem that an Element should not be regarded as an ability, but rather as a process which realizes that ability.

While the developers of RDoC and the Matrix admittedly regard it to be in a nascent state and open to revision, to serve as inspiration for guiding research, if it is to provide the kinds of semantic integration needed for translational research and data sharing, a more consistent method for development should be considered. We contend that the best way to ensure success for future iterations of RDoC and the Matrix is to formalize the Constructs according to established ontological principles, such as those found in the OBO Foundry, ones which are already being used in health informatics solutions.

3 RDOC CONSTRUCTS

RDoC Constructs are described as systems responsible for behaviors. Consider the definition for Approach Motivation, within the Positive Valence Systems Domain:

> A multi-faceted Construct involving mechanisms/processes that regulate the direction and maintenance of approach behavior influenced by pre-existing tendencies, learning, memory, stimulus characteristics, and deprivation states. Approach behavior can be directed toward innate or acquired cues (i.e., unconditioned vs. learned stimuli), implicit or explicit goals; it can consist of goal-directed or Pavlovian conditioned responses.[1]

What does it mean for an entity, a system, a mostly neurological system, to be responsible for some behavior? It is responsible in the sense that the system has, as a result of the way in which it is configured, some disposition towards certain kinds of behavior. This behavior is realized when appropriate environmental conditions and stimuli, both external and internal to the organism, are present. Thus, we take the terms used as RDoC Constructs to refer to bodily systems that bear functions, which are realized in particular kinds of behaviors, ones which ultimately can be observed, described, and measured. These behaviors are those used to diagnose mental dysfunctioning, and which are used as a basis for the criteria in making the traditional categorical diagnoses as seen in the DSM or ICD.

The approach we have adopted is to redefine the RDoC Domains and Constructs as subtypes of 'bodily system', which are defined necessarily by the 'function' they bear. Thus, S is a *bodily system* for organism O if and only if S is an element of O, and S bears a critical function for O, and S is not a part of any other system that has a critical function for O (Smith et al., 2004). For example, the RDoC Construct Approach Motivation redefined:

> 'approach motivation system' $=_{def}$ A positive valence system that bears an approach motivation regulating function.
>
> 'approach motivation regulating function' $=_{def}$ A regulating function that, when realized, is realized in the direction and maintenance of approach behaviors influenced by pre-existing tendencies, learning, memory, stimulus characteristics, and deprivation states.

The advantage of this approach, which we have implemented in OWL as the RDoC Ontology (RDoCOn)[2], is in clearly separating the system as a material entity, most likely a complex aggregate of functionally-related and more granular entities, from the capacity of that system to contribute in some way to the realization of mental processes and behavior. These systems can be composed of circuits, cells, pathways, molecules, and so on. The system can in turn be connected to physiology, which, from the RDoC prospective, is considered as generic biological processes, well-established measures of which have been validated in assessing constructs, such as heart rate or galvanic skin response (Morris and Cuthbert, 2012). Behavior in turn is broader, construed as a combination of more granular physiological processes, many of which are functional psychological processes, such

[1] https://www.nimh.nih.gov/research-priorities/rdoc/constructs/approach-motivation.shtml

[2] https://github.com/mark-jensen/rdocon

as impulsive behavior or joint attention.

However, RDoC currently makes no clear distinction between behavioral paradigms (instances of which would exist on the side of the patient) and assay or testing paradigms (instances of which are planned processes that produce information about the patient). They are currently lumped together in both columns of the Matrix, as either Behavior or Paradigms. A realism-based approach would make this distinction unambiguous and explicit. The advantage is that it would prevent incorrect use of the Matrix, potentially making false assertions, and thus producing false inferences from tools using automated reasoning techniques. For example, RDoC Paradigm Attention Blindness is certainly not a testing paradigm, but rather a complex behavior. While there are tests for measuring attention blindness, such as the invisible gorilla test, the use of the term 'attention blindness' for a Paradigm is ambiguous and could easily lead to problematic results. At an instance level representation of data, it may result in inferring that a behavior of attentional blindness, when asserted as a type of Paradigm, would somehow produce data.

patient_123 participant_in attentionBlindness_123
attentionBlindness_123 has_output dataItem_123

The correct interpretation is where some assay measures the behavior that the patient is participating in, or hypothesized to be. Thus, if this were to be encoded in some knowledge base, the proper sequence would look something like:

patient_123 participant_in attentionBlindness_123
attentionBlindnessAssay_123 has_output dataItem_123
dataItem_123 is_about attentionBlindness_123

Of course, these are patient-level statements, and much of the data relevant to RDoC, especially in regard to genetics, will be about populations of patients that all share some properties in common. We believe this distinction can be adequately addressed, whether through the use of aggregates of patients and processes, or as canonical class-level assertions, restricted to some evidential context, in much in the same way as GO annotations are considered.

4 ONTOLOGIES FOR RDOC

There exist many mid-level ontologies relevant to RDoC: The Gene Ontology (GO), Chemical Entities of Biological Interest (ChEBI), Protein Ontology (PRO), Cell Ontology (CL), Human Phenotype Ontology (HP), Relations Ontology (RO), Neurological Disease Ontology (ND), Neuropsychological Testing Ontology (NPT), Cognitive Paradigm Ontology (COGPO), Evidence Ontology (ECO), Mental Disease Ontology (MDO), Mental Functioning Ontology (MFO), Emotion Ontology (MFOEM), among others.[3] However, gaps exist. Currently no ontology represents the level of granularity for behavioral processes necessary to express all of RDoC's current content. Many of these ontologies are not currently being developed, nor are users documented or curation issues being addressed. Part of our goal in developing RDoCOn is to revitalize, and eventually support the integration of these ontologies. To illustrate this, consider how the results of a study in the genetics related to impulsivity and psychopathology could be represented using ontologies to link the research findings to the RDoC framework, and thus provide the kind of automated discovery and interoperability the NIMH hopes for.

In a recent study (Sanchez-Roige et al., 2017) did a genome-wide association study of delayed discounting, in which the Money Choice Questionnaire was used as a measure of the behavioral paradigm. They found significant association in the intron of GPM6B (Neuronal Membrane Glycoprotein M6B), which has been previously associated with serotonin transport and impulsivity behavior. Looking up GO annotations for GPM6B, we find 85 annotations, 14 of which are for Homo sapiens. GPM6B is associated with a range of GO biological processes, such as *protein transport*, *nervous system development*, *positive regulation of bone mineralization*, and *negative regulation of serotonin uptake*. The last is of interest since previous findings have indicated that lower levels of serotonin are associated with an increase of delayed reward discounting behavior (Schweighofer et al., 2008).

Delayed discounting is the tendency to favor immediate rewards over a (potentially) more valuable distant reward. It is considered an important feature of impulse control, and can be increased, or exaggerated, in people who are diagnosed with mental disorders, such as ADHD, addiction, and depression (Sanchez-Roige et al., 2017). Delayed Discounting in RDoC is listed as an Element under Paradigm and relevant to the Reward Valuation Construct. Our definition of the function associated with Reward Valuation:

> 'reward valuation function' $=_{def}$ An approach motivation function that, when realized, is realized in some mental process that assesses the benefits of a prospective outcome in choosing some reward.

This aligns with RDoC's attempt to link the paradigm as a measure of behavior to the Construct that is responsible for realizing the behavior. However, as noted above, the current version of RDoC often confuses behaviors with the testing paradigms (assays) that measure behaviors. As a behavioral "paradigm", delayed discounting behavior is part of a broader process that realizes a reward valuation function. As an assay "paradigm", a delayed discounting assay process is a planned process of assaying a subject's delayed discounting behavior in a controlled circumstance using some validated instrument, such as a questionnaire, the goal of which is to produce data about the subject's behavior.

[3] For sake of space, we do not include individual citations for these ontologies, but refer to: http://www.obofoundry.org

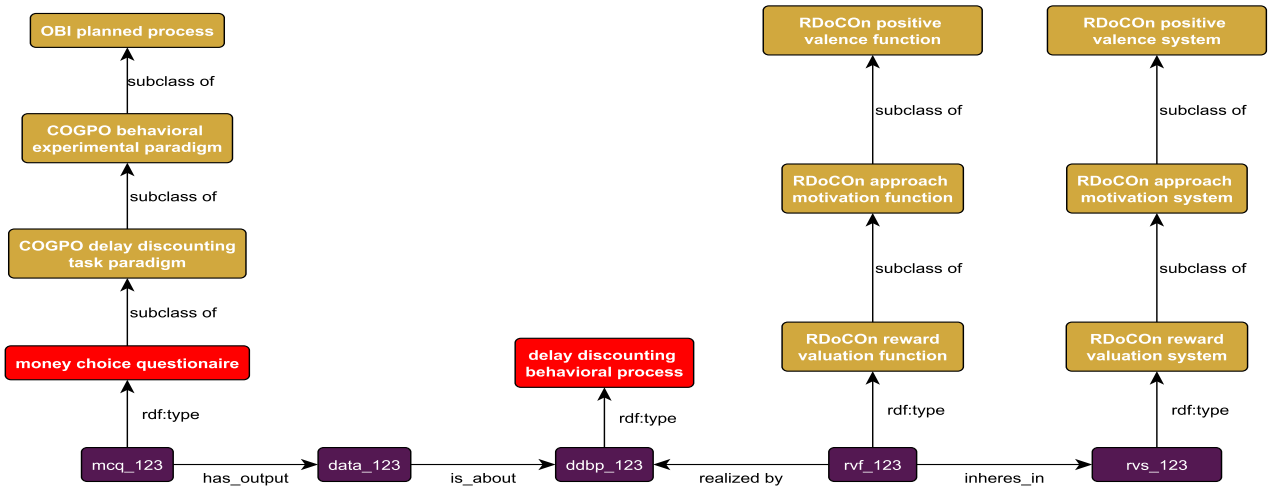

Figure 1. An illustration of how instances of classes will link Constructs to Elements that produce data. Red boxes are for classes that do not exist in a suitable ontology. Instances are given pseudo-identifiers based on abbreviating the name of the class they instantiate.

Looking at existing biomedical knowledge resources, we see MESH defines 'Delayed discounting' as:

> The ability to resist the temptation for an immediate reward and wait for a later reward. The tendency to devalue an outcome as a function of its temporal delay or probability of achievement. It can be evaluated in a psychological paradigm that involves the choice between receiving a smaller immediate reward or a larger delayed reward.[4]

It is defined as an "ability to resist", which puts it within the specifically dependent branch of a BFO hierarchy, most likely as a realizable entity. However, it is asserted as a subclass of 'Choice Behavior', sibling to 'Career Choice, and part of a subsumption hierarchy that does not align with its definition as an ability.

A much better example is found in the Cognitive Paradigm Ontology (COGPO), where 'Delay Discounting Task Paradigm' is defined as "a Behavioral Experimental Paradigm in which, Subjects perform a type of reward task (correct performance is associated with reward, often monetary reward) in which they choose between earning a small reward immediately or a larger reward at a later time" (Turner & Laird, 2012). 'Delay Discounting Task Paradigm' is asserted as a subclass of COGPO 'Behavioral Experimental Paradigm', which is a subclass of the Ontology for Biomedical Investigations (OBI) class 'planned process'. Therefore, all of these "paradigms" in COGPO are processes, instances of which will be assay processes. However, COGPO defines 'Behavioral Experimental Paradigm' rather oddly, as a description of "…the behavioral aspects of the experiment: what stimuli are presented to the subject when, and under what conditions, and what the subject's responses are supposed to be."[5] This definition, which appears to be aligned with that of directive information that specifies how to perform the assay, is contradictory with the textual definitions of the particular subclasses of experimental paradigms and the fact that all are subsumed under the 'planned process' branch of OBI. We assume this is an error on the part of the developers of COGPO, one which confused the specification of a planned process with the process itself.

When representing the study described above (Sanchez-Roige et al., 2017), a class for money choice questionnaire assay process would need to be created since none exists in any ontology. It would be asserted as a subclass of COGPO 'delayed discounting testing paradigm'. However, COGPO's labeling is potentially misleading and could be more explicit, i.e., 'delayed discounting assay process'. The assay process produces data which provides some measure of the behavioral paradigm. (Figure 1).

COGPO does not define the behavioral processes that these behavioral experimental paradigms produce information about. We believe this is appropriate, as terms for representing behavior and mental processes should be maintained in separate ontologies from one that contains classes for assays. This aligns with the OBO Foundry principle of Scope to delineate content and maintain orthogonality with other ontologies.[6] Currently no ontology adequately represents these more granular processes and behaviors, although some appear in the GO, or the Neuro-behavior Ontology. These intermediate processes can be used as way of linking Elements together and ultimately to the Constructs that RDoC intends for consideration as dimensional axes for understanding psychopathology.

[4] http://purl.bioontology.org/ontology/MESH/D065786

[5] http://www.cogpo.org/ontologies/CogPOver1.owl#COGPO_00049

[6] http://www.obofoundry.org/principles/fp-005-delineated-content.html

5 DISCUSSION

The initial stage in the creation of RDoCOn is complete. We have redefined the Constructs and created OWL classes for representing each of the 41 Constructs. They are grouped into five high-level and seven mid-level classes, which mirror the current RDoC taxonomy. We have taken some liberties in our representation of the Constructs. Our goal is to find a balance between the need for ontological rigor, realism-based analysis and development, along with the implementation and eventual use of the ontology. It is important at this stage to maintain close alignment with the current state of RDoC and the Matrix. We are offering RDoCOn as an application ontology to support data integration, query writing, and knowledge discovery in general. It shall serve as a tool to demonstrate the kind of semantic integration that is attainable for research aligned with the RDoC framework by using existing ontologies, especially via the myriad of GO annotations. We consider this a beginning to clearing up the ontological confusion surrounding the RDoC framework. Deeper consideration of the validity of RDoC Constructs and to what extent a strictly realism-based approach can be faithful to the RDoC framework shall continue.

We hope development and use of RDoCOn will promote further development of ontologies related to the mental health domain, such as MFO and COGPO. We would like to see NIMH take note of our efforts and attempt to resolve these issues in the Matrix and underlying RDoC methodology, most notably the lack of clarity and consistency in how the Matrix is constructed. Revision will be needed as RDoC grows and adapts to vetting by the scientific community, potentially even radically altering its organization even as bottom-up data driven approaches are now being considered for reconfiguring the Constructs[7]. RDoCOn, and especially its use and integration with other ontologies, will need formal review by domain specialists as well as by the biomedical ontology community at large.

RDoC is currently under revision and the subject of a numerous articles that both support and criticize the project, its methods and content. There exists a tension amongst the top-down construction of the matrix as it stands, and using bottom-up statistical methods to look for alternate ways of developing functional constructs. Our goal here is not to addressing why or how RDoC was developed Although we have reviewed the content herein and previously, we are not recommending changes to that content, but rather promoting better attention the terminological component of RDoC. We are offering an ontological representation that will facilitate data integration and analysis using RDoC, regardless of how its developers alter the content.

[7] https://www.nimh.nih.gov/about/director/messages/2017/the-future-of-rdoc.shtml

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