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Ontological Realism for the Research Domain Criteria for Mental Disorders

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Abstract. At the heart of the Research Domain Criteria for Mental Disorders is a matrix in which functional aspects of behavior are related to genotypic and (endo-)phenotypic research findings, and the various techniques through which they can been observed. The matrix is work in progress. As such it currently suffers from several shortcomings, the resolution of which, we contend, are essential to success of NIMH's goal of fostering translational science on mental disorders. Using well-established criteria for assessing the terminological and ontological quality of biomedical representations we identified the major problems to be (1) the abundant presence of terms that lack *face value*, (2) the absence of what the exact nature of the represented relationships are, and (3) referential imprecision with respect to the intended granularity of what the terms denote. We propose to eliminate these shortcomings by resorting to definitions and formal representations under the umbrella of Ontological Realism as they already have been developed in the areas of mental health, anatomy and biological functions.

Keywords. RDoC, Mental Disorders, Formal Ontology, Translational Science

1. Introduction

In 2010, the National Institute of Mental Health (NIMH) initiated the Research Domain Criteria (RDoC) project to facilitate translation of modern molecular biology, neuroscience, and behavioral approaches in an attempt to better explain the pathophysiology of mental disorders [1]. At the heart of this project is the development of a matrix in which what are called 'constructs' – some of them being further divided in 'sub-constructs' – are related to what are called 'elements', which are primarily biomarkers, such as genes and molecules, but also findings obtained through, for instance, imaging procedures or standardized questionnaires. The constructs represent functional aspects of behavior most germane to mental disorders such as the ability to receive or produce facial communication, or responsiveness to threat stimuli. They are grouped into five higher-level domains of functioning and reflect contemporary knowledge about major psychological systems: (1) negative valence systems, (2) positive valence systems, (3) cognitive systems, (4) social process systems, and (5) arousal and regulatory systems.

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Table 1. Biomarkers for the sub-construct 'Updating, Representation and Maintenance' of the construct 'Cognitive Control' within the Cognitive Systems domain.

Genes	Molecules	Cells	Circuits	Physiology
COMT, BDNF, DISC1 5HT2A, DRD4, DRD2 5-HTTLPR	Glu, Dopamine, GABA, NE, Acetylcholine	Pyramidal PV	DLPFC PPC Thalamocortical	Gamma synchrony; pupilometry
Behavior	**Self-Reports**		**Paradigms**	
Off-task behaviors; distractibility	Cognitive Failures Questionnaire, Disorganization Sx on SANS/SAPS/ PANSS BRIEF (Gioa)		Task Switching; AX paradigms; Cued stimulus-response reversal tasks; Tower tasks	

The incorporation of motor systems as a 6th domain is currently under debate. The elements are classified in eight groups of what are called 'units of analysis', resp. named *genes*, *molecules*, *cells*, *circuits*, *physiology*, *behaviors*, *self-reports* and *paradigms*. As an example, Table 1 gives an overview of the elements associated thus far with the sub-construct *cognitive control: updating, representation and maintenance* [2].

While the matrix is for now intended to promote the elaboration and validation of clinically relevant mental health constructs and associated measurement approaches, the hope is that it will lead to new classification schemes for mental disorders [3]. A purpose of RDoC is to stimulate research methods which avoid constraints imposed by symptom-based categorizations and synthesize interdisciplinary research in mental disorders. Therefore, the NIMH has created RDoCdb, a data repository designed to harmonize and share research and human subjects data related to RDoC and mental health [4]. Harmonization in this effort is sought by resorting to a Common Data Elements (CDE) paradigm [5]. CDEs are *metadata* constructs that have been developed to reduce time and effort spent by researchers deciding what data elements to use. They are defined in detail in a metadata dictionary so that data elements can be shared in a standardized format across multiple institutions [6]. However, although large collections of CDEs are loosely organized in contexts, they are typically not created or organized on the basis of ontological principles. Such principles require, for instance a clean separation between data and information on the one hand (brain scans, self reports, diagnoses, …), and what these data are about (brain circuits, emotions, disorders, …). They also require representations to be faithful to reality. Ignoring such principles has odd effects as exemplified in the '12-item grit scale', an RDoC approved self-report [7]. The grit-12 scores the ability of a subject to be persistent and focused in pursuit of long-term goals. Subject must rate the degree to which they self-identify with assertions, such as 'New ideas and projects sometimes distract me from previous ones'. The CDE-enabled version of the grit-12 specifies for the CDE 'interview-age': '*Age is rounded to chronological month. If the research participant is 15-days-old at time of interview, the appropriate value would be 0 months. If the participant is 16-days-old, the value would be 1 month*'.

2. Methods

The purpose of the work presented here was to assess the extent to which the matrix is congruent with terminological and ontological principles and to provide suggestions for remediation to better serve clinical and translational research in mental health. The matrix was browsed as available in [2] during October 2016. To make analysis easier,

all constructs and elements were copied into a single spreadsheet, thereby preserving their respective classification in functional domains and units of analysis as well as the definitions and explanations provided. Terms and definitions were then evaluated in function of well-known quality assessment criteria and recommendations for terminologies [8] and ontologies [9] such as face validity of terms, fixed meaning, clean separation of subsumption relations from other relations, etc. Deviations thereof were classified in coherent groups. Finally, a further literature study was conducted to identify ontological theories that could serve as candidates for adding more rigor to the matrix.

3. Results

A major problem with the current incarnation of the RDoC matrix is that for several *element* terms it is hard to assess whether they lack face value – i.e. the display term does not capture what is meant – or are erroneously classified. We found that 12 elements, e.g. dopamine and norepinephrine, appear in columns for both *genes* and *molecules* units of analysis. Clearly, nothing which is a gene can also be a molecule. The terms, when appearing under *genes*, might perhaps mean something like 'genes encoding proteins which are part of the pathway which synthesizes dopamine' or 'genes encoding receptors for dopamine'. Other examples are the presence of 'cannabinoid system', 'opioid system' and 'mouse knockout models' under *genes*, but how can a system or a model be a gene?

A second problem is that most pages accessible through [2] omit to specify what exactly are the relationships between the elements on the one hand, and the constructs and units of analysis on the other hand. Few contain references to one or more papers but without annotations from the latter to the former. More detail was provided in an earlier version of the matrix [10], what allowed us to conclude that the relationships are indeed quite diverse. For example, for the construct 'Loss', defined *as 'a state of deprivation of a motivationally significant con-specific, object, or situation*', we find in the matrix version in [2] the molecules 'glucocorticoid receptors' and 'CRH', whereas the version in [10] refers explicitly to '**down**regulation of glucocorticoid receptors' and '**up**regulation of CRH' [bold emphases added]. This is, once more, an example of the violation of the terminological principle that terms should have face value [8].

A third problem is the lack of referential precision and the overlap amongst the various units of analysis, and amongst these units and the constructs, in part caused by this imprecision. Why does the matrix refer to 'neurons' as elements under 'cells' as this seems to be too vague a cell-type in the context of mental disorders, applicable to most constructs? Yet it is only associated with 'acute threat: fear'. There is also overlap between cells and circuits, circuits and physiology, and between all of these and the constructs themselves. This is because the constructs are not well defined enough to unravel this overlap. 'Animacy perception', e.g., is a sub-construct defend as 'the ability to appropriately perceive that another entity is an agent (has a face, interacts contingently, exhibits biological motion)', while the term 'ability to appropriately attribute animacy to other agents' is used as an element belonging to the unit of analysis 'Behavior'.

4. Discussion

The RDoC initiative is a clear move away from the phenomenological "lumping" approach of the Diagnostic and Statistical Manual of Mental Disorders (DSM) and aims

to integrate a more dimensional approach anchored in neuroscience [1, 11]. It is acknowledged that it is work in progress, and that refinement is needed [3]. Our analysis indicates that there is a need for this refinement and to adopt formal ontological principles as already have been suggested in the domain of mental health [12-14].

A first step would be to reformulate the definitions of RDoC constructs and the domains under which they are classified along the lines of 'bodily systems' [15]:

X is a bodily system for organism Y if and only if: (D1)

(i) X is an element of Y;

(ii) X has a critical function for Y;

(iii) X is not a part of any other system that has a critical function for Y.

F is a critical function for system Y if and only if: (D2)

(i) some element X of Y has F as its function;

(ii) the continued functioning of system Y is causally dependent on the continued performing of F by X.

Clause (ii) in D1 offers a perspective to express formally what the functions of the systems represented by the constructs are, as well as the relationships with the various units of analysis by means of which the realization of these functions and the participation of molecules, genes, cells and circuits therein can be measured. Furthermore, the fact that bodily systems are defined in relation to critical functions, does not mean they are not related also to other functions that are not critical. Adherence to clause (iii) can reduce the observed overlap in parallel with a formal description of the parthood relationships between cells, circuits and bodily systems as represented in the FMA [16]. Caution is required, however, since D1, because of clause (iii), reserves the term 'bodily system' for the highest level systems with respect to parthood. Mapping the RDoC constructs and sub-constructs to bodily systems in the D1 sense requires thus a certain ontological commitment on behalf of the RDoC-matrix authors with respect to the precise relationships between constructs and the domain they belong to, and between sub-constructs and the constructs of which they are declared to be sub-constructs of. For example, the use of the plural in the domain 'Negative Valence Systems' suggests that the constructs 'Acute Threat ("Fear")' and 'Potential Threat ("Anxiety")' are distinct ***types*** of negative valence systems, and not ***parts*** of what would be '***the*** negative valence system' of the human body (as in 'the circulatory system'). However, how the sub-constructs 'Reward Valuation' and 'Effort Valuation / Willingness to Work' ontologically relate to the construct 'Approach Motivation', which they appear under – as parts or types, if they are systems at all and not functions – can only be determined via careful analysis by ontologists in collaboration with neuroscientists.

A second step would be to improve how various 'elements' are grouped in the matrix by defining explicitly the eight 'units of analysis', in function of what it means to be an element as defined in the context of the bodily systems and subsystems of organisms [15] (the use of the term 'element' in both [15] and the RDoC-matrix is coincidental):

X is an element of Y if and only if: (D3)

(i) X and Y are parts of an organism;

(ii) X is lower on the spatial-functional hierarchy than the organism as a whole, and lower than the system of which it is an element;

(iii) X has one or more specific functions;

(iv) X is causally relatively isolated from the parts of the organism that surround it;

(v) X is maximal, in the sense that it is not a proper part of any item on the same level of the spatial-functional hierarchy satisfying (i) to (iv).

5. Conclusion

The RDoC initiative has been received both with enthusiasm (by neuroscientists) and skepticism (by traditional psychiatrists) and several caveats have been raised from within the domain [3], primarily for how the matrix is organized and the lack of expressiveness. We demonstrated that present qualms are not ungrounded, but that improvements can be achieved by applying appropriate terminological and ontological principles grounded in Ontological Realism. Needed steps are refinement of the constructs and units of analysis, to formalize their ontological foundation, as we have exemplified by our proposal to resort to a formal definition for bodily system. Such formalization is essential for data harmonization. However, this requires a close collaboration between psychiatrists, psychologists and neuroscientists on the one hand, and ontologists on the other.

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